# Testing, Evaluation, and Monitoring of Hepatitis C

The following pages regard pre- and post-treatment of patients with HCV:



# HCV Testing and Linkage to Care

## Recommendations for One-time HCV Testing

| RECOMMENDED | RATING |
|---|---|
| One-time HCV testing is recommended for persons born between 1945 and 1965,* without prior ascertainment of risk. | I, B |
| Other persons should be screened for risk factors for HCV infection, and one-time testing should be performed for all persons with behaviors, exposures, and conditions associated with an increased risk of HCV infection.<br><br>1. **Risk behaviors**<br>◦ Injection-drug use (current or ever, including those who injected once)<br>◦ Intranasal illicit drug use<br><br>2. **Risk exposures**<br>◦ Persons on long-term hemodialysis (ever)<br>◦ Persons with percutaneous/parenteral exposures in an unregulated setting<br>◦ Healthcare, emergency medical, and public safety workers after needlesticks, sharps, or mucosal exposures to HCV-infected blood<br>◦ Children born to HCV-infected women<br>◦ Prior recipients of transfusions or organ transplants, including persons who:<br>▪ Were notified that they received blood from a donor who later tested positive for HCV infection<br>▪ Received a transfusion of blood or blood components, or underwent an organ transplant before July 1992<br>▪ Received clotting factor concentrates produced before 1987<br>◦ Persons who were ever incarcerated<br><br>3. **Other considerations**<br>◦ HIV infection<br>◦ Sexually active persons about to start pre-exposure prophylaxis (PreP) for HIV<br>◦ Unexplained chronic liver disease and/or chronic hepatitis including elevated alanine aminotransferase levels | I, B |

| Recommendations for One-time HCV Testing | |
|---|---|
| ◦ Solid organ donors (deceased and living) | |
| * Regardless of country of birth | |

There are an estimated 3.5 million HCV-infected persons in the United States, 2.7 million in the general non-institutionalized population (Denniston, 2014), plus an additional 800,000 incarcerated, institutionalized, or homeless (Edlin, 2015); about half of all infected people are unaware they are infected (Denniston, 2012); (Holmberg, 2013).

HCV testing is recommended in select populations based on demography, prior exposures, high-risk behaviors, and medical conditions. Recommendations for testing are based on HCV prevalence in these populations, proven benefits of care and treatment in reducing the risk of hepatocellular carcinoma and all-cause mortality, and the potential public health benefit of reducing transmission through early treatment, viral clearance, and reduced risk behaviors (Smith, 2012); (USPSTF, 2013); (CDC, 1998).

HCV is primarily transmitted through percutaneous exposure to blood. Other modes of transmission include mother-to-infant and contaminated devices shared for noninjection drug use; sexual transmission also occurs but generally seems to be inefficient except among HIV-infected men who have unprotected sex with men (Schmidt, 2014). The most important risk for HCV infection is injection drug use, accounting for at least 60% of acute HCV infections in the United States. Healthcare exposures are important sources of transmission, including the receipt of blood products before 1992 (after which routine screening of blood supply was implemented), receipt of clotting factor concentrates before 1987, long-term hemodialysis, needlestick injuries among healthcare workers, and patient-to-patient transmission resulting from poor infection control practices. Other risk factors include having been born to an HCV-infected mother, having been incarcerated, and percutaneous or parenteral exposures in an unregulated setting: examples are tattoos received outside of licensed parlors and medical procedures done internationally or domestically where strict infection control procedure may not have been followed (eg surgery before the implementation of universal precautions) (Hellard, 2004).

The importance of these risk factors might differ based on geographic location and population (USPSTF, 2013); (CDC, 1998). An estimated 29% of incarcerated persons in North America are anti-HCV positive, supporting the recommendation to test this population for HCV (Larney, 2013). Because of shared transmission modes, persons with HIV infection are at risk for HCV; sexual transmission is a particular risk for HIV-infected men who have unprotected sex with men (Hosein, 2013); (van de Laar, 2010). Screening sexually active non-HIV-infected persons before they start pre-exposure prophylaxis (PreP) for prevention of HIV infection should also be considered (Volk, 2015). Recent data also support testing in all deceased and living solid-organ donors because of the risk of HCV infection posed to the recipient (Seem, 2013); (Lai, 2013). Although Centers for Disease Control and Prevention (CDC) and US Preventive Services Task Force hepatitis C testing guidelines do not specifically recommend testing immigrants from countries with a high prevalence (eg, Egypt or Pakistan) of hepatitis C virus infection, such persons should be tested if they were born from 1945 through 1965 or if they have risk factors (listed in Summary Box) for infection.

In 2012, CDC expanded its guidelines originally issued in 1998 (CDC, 1998) for risk-based HCV testing with a recommendation to offer a one-time (see Summary Box) HCV test to all persons born from 1945 through 1965, without prior ascertainment of HCV risk-factors. This recommendation was supported by evidence demonstrating that a risk-based strategy alone failed to identify more than 50% of HCV infections in part due to patient underreporting of their risk and provider limitations in ascertaining risk-factor information. Furthermore, persons in the 1945 to 1965 birth cohort accounted for nearly three-fourths of all HCV infections, with a five-times higher prevalence (3.25%) than other persons, reflecting a higher incidence of HCV infections in the 1970s and 1980s (peaking at 230,000, compared with 15,000 in 2009). A recent retrospective review showed that 68% of persons with HCV infection would have been identified through a birth cohort testing strategy, whereas only 27% would have been screened with the risk-based approach (Mahajan, 2013). The cost-effectiveness of one-time birth cohort testing is comparable to that of current risk-based screening strategies (Smith, 2012).

CDC and the US Preventive Services Task Force (USPSTF) both recommend a one-time HCV test in asymptomatic

persons belonging to the 1945 to 1965 birth cohort and other persons based on exposures, behaviors, and conditions that increase risk for HCV infection.

## Recommendation for HCV Testing Those with Ongoing Risk Factors

| RECOMMENDED | RATING |
|---|---|
| Annual HCV testing is recommended for persons who inject drugs and for HIV-seropositive men who have unprotected sex with men. Periodic testing should be offered to other persons with ongoing risk factors for exposure to HCV. | IIa, C |

Evidence regarding the frequency of testing in persons at risk for ongoing exposure to HCV is lacking; therefore, clinicians should determine the periodicity of testing based on the risk of reinfection. Because of the high incidence of HCV infection among persons who inject drugs and among HIV-infected MSM who have unprotected sex (Aberg, 2014); (Linas, 2012); (Wandeler, 2012); (Witt, 2013); (Bravo, 2012); (Williams, 2011), at least annual HCV testing is recommended in these subgroups.

Implementation of clinical decision support tools or prompts for HCV testing in electronic health records could facilitate reminding clinicians of HCV testing when indicated (Hsu, 2013); (Litwin, 2012); (http://nvhr.org/EMR).

## Recommendations for Follow-up of Initial Testing

| RECOMMENDED | RATING |
|---|---|
| An anti-HCV test is recommended for HCV testing, and if the result is positive, current infection should be confirmed by a sensitive HCV RNA test. | I, A |
| Among persons with a negative anti-HCV test who are suspected of having liver disease, testing for HCV RNA or follow-up testing for HCV antibody is recommended if exposure to HCV occurred within the past six months; testing for HCV RNA can also be considered in persons who are immunocompromised. | I, C |
| Among persons at risk of reinfection after previous spontaneous or treatment-related viral clearance, initial HCV-RNA testing is recommended because an anti-HCV test is expected to be positive. | I, C |
| Quantitative HCV-RNA testing is recommended prior to the initiation of antiviral therapy to document the baseline level of viremia (ie, baseline viral load). | I, A |
| Testing for HCV genotype is recommended to guide selection of the most appropriate antiviral regimen. | I, A |
| If found to have positive results for anti-HCV test and negative results for HCV RNA by polymerase chain reaction (PCR), persons should be informed that they do not have evidence of current (active) HCV infection. | I, A |

All persons recommended for HCV testing should first be tested for HCV antibody (anti-HCV) (CDC, 2013); (Alter, 2003) using an FDA-approved test. FDA-approved tests include laboratory-based assays and a point-of-care assay (ie, OraQuick HCV Rapid Antibody Test [OraSure Technologies]) (Lee, 2011). The latter is an indirect immunoassay with a sensitivity and specificity similar to those of FDA-approved laboratory-based HCV antibody assays.

A positive test result for anti-HCV indicates either current (active) HCV infection (acute or chronic), past infection that has resolved, or a false-positive test result (Pawlotsky, 2002). Therefore, an HCV nucleic acid test (NAT) to detect viremia is necessary to confirm current (active) HCV infection and guide clinical management, including initiation of HCV treatment. HCV RNA testing should also be performed in persons with a negative anti-HCV test who are either immunocompromised (eg, persons receiving chronic hemodialysis) (KDIGO, 2008) or who might have been exposed to HCV within the last six months because these persons may be anti-HCV negative. An HCV RNA test is also needed to detect reinfection in anti-HCV–positive persons after previous spontaneous or treatment-related viral clearance.

An FDA-approved quantitative or qualitative NAT with a detection level of 25 IU/mL or lower should be used to detect HCV RNA. Testing and Linkage to Care Table 1 lists FDA-approved, commercially available anti-HCV screening assays. Testing and Linkage to Care Figure 1 shows the CDC-recommended testing algorithm.

Persons who have positive results for an anti-HCV test and negative results for HCV RNA by polymerase chain reaction (PCR) should be informed that they do not have laboratory evidence of current (active) HCV infection. Additional HCV testing is typically unnecessary. The HCV RNA test can be repeated when there is a high index of suspicion for recent infection or in patients with ongoing risk factors for HCV infection.

Practitioners or persons may seek additional testing to learn if the HCV antibody test represents a remote HCV infection that has resolved or a false-positive result. For patients with no apparent risk for HCV infection, the likelihood of a false-positive HCV antibody test is directly related to the HCV prevalence in the tested population; false-positive test results for anti-HCV are most common for populations with a low prevalence of HCV infection (Alter, 2003). If further testing is desired to distinguish between true positivity and biologic false positivity for HCV antibody, testing may be done with a second FDA-approved HCV antibody assay that is different from the assay used for initial antibody testing. A biologic false result should not occur with two different tests (Vermeersch, 2008); (CDC, 2013). Prior to the initiation of HCV therapy, quantitative HCV RNA testing may be used to determine the baseline level of viremia (ie, viral load) in order to define the duration of treatment for certain regimens. The degree of viral load decline after initiation of treatment is less predictive of sustained virologic response in the era of direct-acting antiviral therapy (see Pretreatment and On-Treatment Monitoring). Testing for HCV genotype helps to guide selection of the most appropriate treatment regimen.

## Recommendations for Counseling Those with Current (Active) HCV Infection

| RECOMMENDED | RATING |
|---|---|
| Persons with current (active) HCV infection should receive education and interventions aimed at reducing progression of liver disease and preventing transmission of HCV. | IIa, B |
| 1. Abstinence from alcohol and, when appropriate, interventions to facilitate cessation of alcohol consumption should be advised for all persons with HCV infection. | IIa, B |
| 2. Evaluation for other conditions that may accelerate liver fibrosis, including HBV and HIV infections, is recommended for all persons with HCV infection. | IIb, B |
| 3. Evaluation for advanced fibrosis using liver biopsy, imaging, and/or noninvasive markers is recommended for all persons with HCV infection, to facilitate an appropriate decision regarding HCV treatment strategy and to determine the need for initiating additional measures for the management of cirrhosis (eg, hepatocellular carcinoma screening) (see When and in Whom to Initiate HCV Therapy). | I, A |
| 4. Vaccination against hepatitis A and hepatitis B is recommended for all susceptible persons with HCV infection. | IIa, C |
| 5. Vaccination against pneumococcal infection is recommended to all patients with cirrhosis (Marrie, 2011). | IIa, C |

## Recommendations for Counseling Those with Current (Active) HCV Infection

| | |
|---|---|
| 6. All persons with HCV infection should be provided education on how to avoid HCV transmission to others. | I, C |

In addition to receiving therapy, HCV-infected persons should be educated about how to prevent further damage to their liver. Most important is prevention of the potential deleterious effect of alcohol. Numerous studies have found a strong association between the use of excess alcohol and the development or progression of liver fibrosis and the development of hepatocellular carcinoma (Poynard, 1997); (Harris, 2001); (Wiley, 1998); (Corrao, 1998); (Bellentani, 1999); (Noda, 1996); (Safdar, 2004).

The daily consumption of more than 50 grams of alcohol has a high likelihood of worsening fibrosis. Some studies indicate that daily consumption of smaller amounts of alcohol also has a deleterious effect on the liver; however, these data are controversial (Westin, 2002). Excess alcohol intake may also cause steatohepatitis. Alcohol screening and brief interventions such as those outlined by the National Institute of Alcohol Abuse and Alcoholism (http://pubs.niaaa.nih.gov/publications/Practitioner/CliniciansGuide2005/clinicians_guide.htm) have been demonstrated to reduce alcohol consumption and episodes of binge drinking in the general population and among HCV-infected persons who consume alcohol heavily (Whitlock, 2004); (Dieperink, 2010); (Proeschold-Bell, 2012). Persons identified as abusing alcohol and having alcohol dependence require treatment and consideration for referral to an addiction specialist.

Hepatitis B virus (HBV) and human immunodeficiency virus-1 (HIV) coinfection have been associated with poorer prognosis of HCV in cohort studies (Thein, 2008a); (Zarski, 1998). Owing to overlapping risk factors for these infections and additional benefits of their identification and treatment, persons with HCV should be tested for HIV antibody and hepatitis B surface antigen (HBsAg) using standard assays for screening (Moyer, 2013); (CDC, 2008); (http://www.aafp.org/afp/2008/0315/p819.html and http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5708a1.htm) and counseled on how to reduce their risk of acquiring these infections, including through HBV vaccination (see below).

Patients with obesity and metabolic syndrome having underlying insulin resistance are more prone to have nonalcoholic fatty liver disease, which is a risk factor for fibrosis progression in HCV-infected persons (Hourigan, 1999); (Ortiz, 2002). Therefore, HCV-infected persons who are overweight or obese (defined by a body mass index 25 $kg/m^2$ or higher or 30 $kg/m^2$ or higher, respectively) should be counseled regarding strategies to reduce weight and improve insulin resistance via diet, exercise, and medical therapies (Musso, 2010); (Shaw, 2006). Patients with HCV infection and hyperlipidemia or cardiovascular comorbidities may also benefit from various hypolipidemic drugs. Prospective studies have demonstrated the safety and efficacy of statins in patients with chronic HCV and others with compensated chronic liver disease (Lewis, 2007). Therefore, these agents should not be withheld in HCV-infected patients.

The severity of liver disease associated with chronic HCV infection is a key factor in determining the initial and follow-up evaluation of patients. Although patients with more advanced disease may have a lower response to HCV therapy, they are also most likely to derive the greatest survival benefit (Ghany, 2011). A liver biopsy can provide objective, semiquantitative information regarding the amount and pattern of collagen or scar tissue in the liver that can assist with treatment and monitoring plans. The Metavir fibrosis score (F0-F4) and Ishak fibrosis score (0-6) are commonly used to score the amount of hepatic collagen. A liver biopsy can also help assess the severity of liver inflammation, or of hepatic steatosis, and help exclude competing causes of liver injury (Kleiner, 2005). However, the procedure has a low but real risk of complications, and sampling artifact makes its serial use in most patients less desirable (Regev, 2002). Noninvasive methods frequently used to estimate liver disease severity include a liver-directed physical exam (normal in most patients), routine blood tests (eg, serum alanine aminotransferase [ALT] and aspartate aminotransferase [AST], albumin, bilirubin, international normalized ratio levels, and complete blood cell counts with platelets), serum fibrosis marker panels, liver imaging (eg, ultrasound, computed tomography scan), and transient elastography. Simple blood tests (eg, serum AST-to-platelet ratio index [APRI]) (Wai, 2003); (http://www.hepatitisc.uw.edu/page/clinical-calculators/apri), FIB-4, (Sterling, 2006) and assessment of liver surface nodularity and spleen size by liver ultrasound or other cross-sectional imaging modalities can help determine if patients with HCV have occult portal hypertension, which is associated

with a greater likelihood of developing future hepatic complications in untreated patients (Chou, 2013); (Rockey, 2006). Liver elastography can provide instant information regarding liver stiffness at the point of care and can reliably distinguish patients with a high versus low likelihood of cirrhosis (Castera, 2012); (Bonder, 2014). A more detailed discussion regarding fibrosis assessment is found in the section When and In Whom to Initiate Therapy. Because persons with known or suspected bridging fibrosis and cirrhosis are at increased risk of developing complications of advanced liver disease, they require more frequent follow-up; these persons should also avoid hepatotoxic drugs (eg, excessive acetaminophen [ie, >2 g/d] or certain herbal supplements) or nephrotoxic drugs (eg, nonsteroidal antiinflammatory drugs) and receive ongoing imaging surveillance for liver cancer and gastroesophageal varices (Sangiovanni, 2006); (Fontana, 2010). Persons with cirrhosis are also more susceptible to invasive pneumococcal infection (Marrie, 2011) and should receive pneumococcal vaccination (CDC, 2012).

Exposure to infected blood is the primary mode of HCV transmission. HCV-infected persons must be informed of the precautions needed to avoid exposing others to infected blood. This is particularly important for persons who use injection drugs, given that HCV transmission in this population primarily results from the sharing of needles and other infected implements. Recently, epidemics of acute HCV due to sexual transmission in HIV-infected men who have sex with men have also been described (van de Laar, 2009); (Urbanus, 2009); (Fierer, 2008). Testing and Linkage to Care Table 2 outlines measures to avoid HCV transmission. HCV is not spread by sneezing, hugging, holding hands, coughing, or sharing eating utensils or drinking glasses, nor is it transmitted through food or water.

## Recommendation for Linkage to Care

| RECOMMENDED | RATING |
|---|---|
| All persons with current active HCV infection should be linked to a practitioner who is prepared to provide comprehensive management. | IIa, C |

Improvement in identification of current (active) HCV infection and advances in treatment regimens will have limited impact on HCV-related morbidity and mortality without concomitant improvement in linkage to care. All patients with current HCV infection and a positive HCV RNA test result, should be evaluated by a practitioner with expertise in assessment of liver disease severity and HCV treatment. Subspecialty care and consultation are required for persons with HCV infection who have advanced fibrosis or cirrhosis (stage F3 or above on Metavir scale), including possible referral for consideration of liver transplantation. In the United States, only an estimated 13% to 18% of HCV-infected persons had received treatment by 2013 (Holmberg, 2013). Lack of appropriate practitioner assessment and delays in linkage to care can result in negative health outcomes. Further, patients who are lost to follow-up fail to benefit from evolving evaluation and treatment options.

Commonly cited patient-related barriers to treatment initiation include contraindications to treatment (eg, medical or psychiatric comorbidities), lack of acceptance of treatment (eg, asymptomatic nature of disease, competing priorities, low treatment efficacy, and long treatment duration and adverse effects), and lack of access to treatment (eg, cost and distance to specialist) (Khokhar, 2007); (Arora, 2011); (Clark, 2012). Common practitioner-related barriers include perceived patient-related barriers (eg, fear of adverse effects, treatment duration, cost, and effectiveness), lack of expertise in HCV treatment, lack of specialty referral resources, resistance to treating persons currently using illicit drugs or alcohol, and concern about cost of HCV treatment (Morrill, 2005); (Reilley, 2013); (McGowan, 2013). Data are lacking to support exclusion of HCV-infected persons from considerations for hepatitis C therapy based on the amount of alcohol intake or the use of illicit drugs. Based on data from IFN-based treatment, SVR rates among people who inject drugs are comparable to those among people who do not inject drugs (Aspinall, 2013). Some possible strategies to address these barriers are listed in Testing and Linkage to Care Table 3. One strategy that addresses several barriers is colocalization or integrated care of HCV screening, evaluation, and treatment with other medical or social services. Colocalization has already been applied to settings with a high prevalence of HCV infection (eg, correctional facilities and programs providing needle exchange, substance abuse treatment, and methadone maintenance) but is not uniformly available (Islam, 2012); (Stein, 2012); (Bruggmann, 2013). Integrated care, consisting of multidisciplinary care coordination and patient case management, increased the proportion of patients with HCV infection and psychiatric illness or substance use who begin

antiviral therapy and achieve an SVR, without serious adverse events (Ho, 2015).

A strategy that addresses lack of access to specialists (a primary barrier to hepatitis C care) is participation in models involving close collaboration between primary care practitioners and subspecialists (Arora, 2011); (Rossaro, 2013); (Miller, 2012). Such collaborations have used telemedicine and knowledge networks to overcome geographic distances to specialists (Arora, 2011); (Rossaro, 2013). For example, Project ECHO (Extension for Community Healthcare Outcomes [http://echo.unm.edu]) uses videoconferencing to enhance primary care practitioner capacity in rendering HCV care and treatment to New Mexico's large rural and underserved population (Arora, 2011). Through case-based learning and real-time feedback from a multidisciplinary team of specialists (ie, gastroenterology, infectious diseases, pharmacology, and psychiatry practitioners), Project ECHO has expanded access to HCV infection treatment in populations that might have otherwise remained untreated. The short duration of therapy and few serious adverse events related to the new hepatitis C medications present an opportunity to expand the number of mid-level practitioners and primary care physicians in the management and treatment of HCV infection.

Additional strategies for enhancing linkage to and retention in care could be adapted from other fields, such as tuberculosis and HIV. For example, use of directly observed therapy has enhanced adherence to tuberculosis treatment, and use of case managers and patient navigators has reduced loss of follow-up in HIV care (Govindasamy, 2012). Recent hepatitis C test and care programs have identified the use of patient navigators or care coordinators to be an important intervention in overcoming challenges to linkage to, and retention in care (Trooskin, 2015); (Coyle, 2015). Ongoing assessment of efficacy and comparative effectiveness of this and additional strategies is a crucial area of future research for patients with HCV infection. Replication and expansion of best practices and new models for linkage to HCV care will also be crucial to maximize the public health impact of newer treatment paradigms.

**Last update:** July 6, 2016

## Testing and Linkage to Care: Table 1 - FDA-approved, Commercially Available Anti-HCV Screening Assays

| Assay | Manufacturer | Format |
|---|---|---|
| Abbott HCV EIA 2.0 | Abbott Laboratories, Abbott Park, IL, USA | EIA (Manual) |
| Advia Centaur HCV | Siemens, Malvern, PA, USA | CIA (Automated) |
| ARCHITECT Anti-HCV | Abbott Laboratories, Abbott Park, IL, USA | CMIA (Automated) |
| AxSYM Anti-HCV | Abbott Laboratories, Abbott Park, IL, USA | MEIA (Automated) |
| OraQuick HCV Rapid Antibody Test | OraSure Technologies, Inc, Bethlehem, PA, USA | Immunochromatographic (Manual) |
| Ortho HCV Version 3.0 EIA | Ortho | EIA (Manual) |

| Assay | Manufacturer | Format |
|---|---|---|
| VITROS Anti-HCV | Ortho | CIA (Automated) |

Anti-HCV, HCV antibody; EIA, enzyme immunoassay; CIA, chemiluminescent immunoassay; MEIA, microparticle enzyme immunoassay; CMIA, chemiluminescent microparticle immunoassay.

Table prepared by Saleem Kamili, PhD, Centers for Disease Control and Prevention.

**Last update:** Reviewed June 2016

## Testing and Linkage to Care: Table 2 - Measures to Prevent Transmission of HCV

- Persons with HCV infection should be counseled to avoid sharing toothbrushes and dental or shaving equipment, and be cautioned to cover any bleeding wound to prevent the possibility of others coming into contact with their blood.
- Persons should be counseled to stop using illicit drugs and enter substance abuse treatment. Those who continue to inject drugs should be counseled to avoid reusing or sharing syringes, needles, water, cotton, and other drug preparation equipment; use new sterile syringes and filters and disinfected cookers; clean the injection site with a new alcohol swab; and dispose of syringes and needles after one use in a safe, puncture-proof container.
- Persons with HCV infection should be advised not to donate blood and to discuss HCV serostatus prior to donation of body organs, other tissue, or semen.
- Persons with HIV infection and those with multiple sexual partners or sexually transmitted infections should be encouraged to use barrier precautions to prevent sexual transmission. Other persons with HCV infection should be counseled that the risk of sexual transmission is low and may not warrant barrier protection.
- Household surfaces and implements contaminated with visible blood from an HCV-infected person should be cleaned using a dilution of 1 part household bleach to 9 parts water. Gloves should be worn when cleaning up blood spills.

**Last update:** Reviewed June 2016

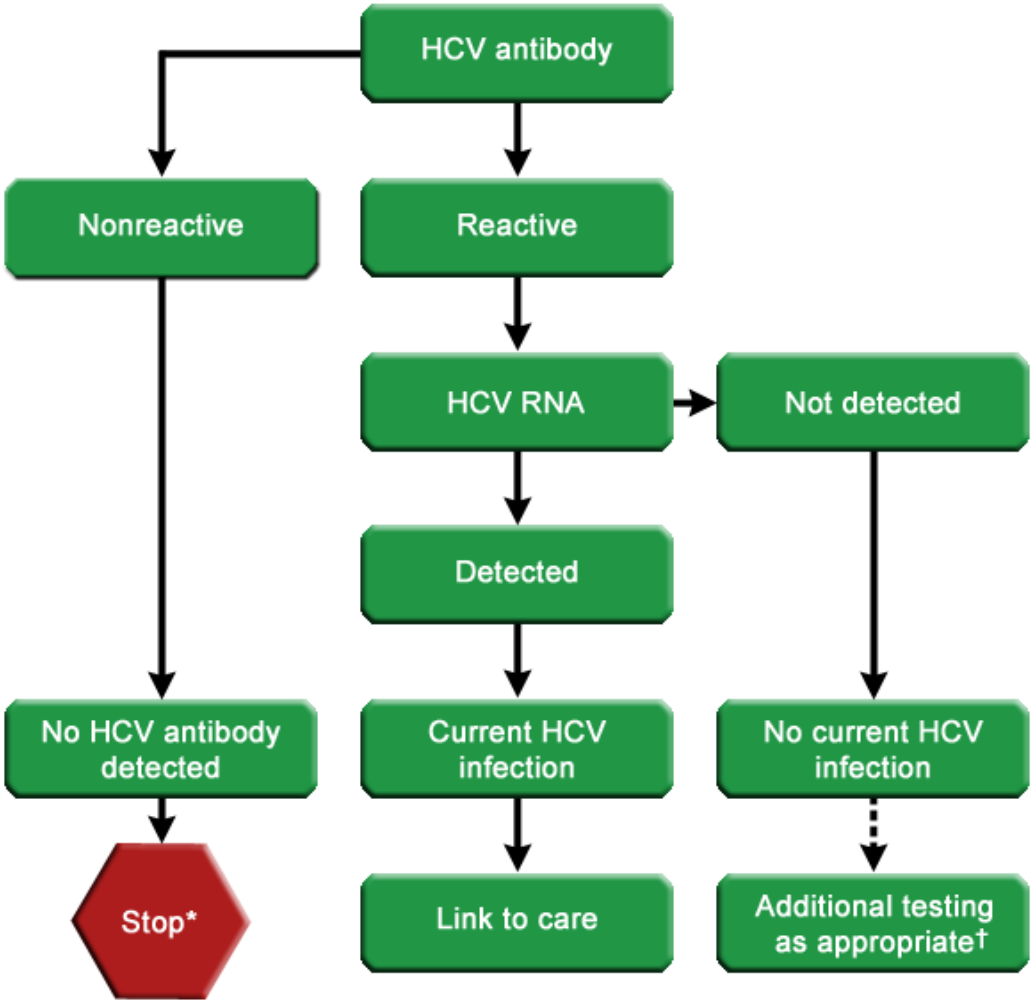
## Testing and Linkage to Care: Table 3 - Common Barriers to HCV Treatment and Potential Strategies

| Barrier | Strategy |
|---|---|
| Contraindications to treatment (eg, | • Counseling and education |

| Barrier | Strategy |
|---|---|
| comorbidities, substance abuse, and psychiatric disorders) | • Referral to services (eg, psychiatry and opioid substitution therapy)<br>• Optimize treatment with simpler and less toxic regimens |
| Competing priority and loss to follow-up | • Conduct counseling and education<br>• Engage case managers and patient navigators (HIV model)<br>• Co-localize services (eg, primary care, medical homes, and drug treatment) |
| Long treatment duration and adverse effects | • Optimize treatment with simpler and better tolerated regimens<br>• Education and monitoring<br>• Directly observed therapy (tuberculosis model) |
| Lack of access to treatment (high cost, lack of insurance, geographic distance, and lack of availability of specialists) | • Leverage expansion of coverage through the Patient Protection and Affordable Care Act<br>• Participate in models of care involving close collaboration between primary care practitioners and specialists<br>• Pharmaceutical patient assistance programs<br>• Co-localize services (primary care, medical homes, drug treatment) |
| Lack of practitioner expertise | • Collaboration with specialists (eg, via Project ECHO-like models and telemedicine)<br>• Develop accessible and clear HCV treatment guidelines<br>• Develop electronic health record performance measures and clinical decision support tools (eg, pop-up reminders and standing orders) |

**Last update:** Reviewed June 2016

## Testing and Linkage to Care: Figure 1 - CDC Recommended Testing Sequence for Identifying Current HCV Infection




* For persons who might have been exposed to HCV within the past 6 months, testing for HCV RNA or follow-up testing for HCV antibody should be performed. For persons who are immunocompromised, testing for HCV RNA should be performed.

† To differentiate past, resolved HCV infection from biologic false positivity for HCV antibody, testing with another HCV antibody assay can be considered. Repeat HCV RNA testing if the person tested is suspected to have had HCV exposure within the past 6 months or has clinical evidence of HCV disease, or if there is concern regarding the handling or storage of the test specimen.

Adapted from Centers for Disease Control and Prevention (CDC), 2013 (CDC, 2013).

**Last update:** Reviewed June 2016

## When and in Whom to Initiate HCV Therapy

Successful hepatitis C treatment results in sustained virologic response (SVR), which is tantamount to virologic cure, and as such, is expected to benefit nearly all chronically infected persons. When the US Food and Drug Administration (FDA) approved the first IFN-sparing treatment for HCV infection, many patients who had previously been “warehoused” sought treatment, and the infrastructure (experienced practitioners, budgeted health-care dollars, etc) did not yet exist to treat all

patients immediately. Thus, the panel offered guidance for prioritizing treatment first to those with the greatest need. Since that time, there have been opportunities to treat many of the highest-risk patients and to accumulate real-world experience of the tolerability and safety of newer HCV medications. More importantly, from a medical standpoint, data continue to accumulate that demonstrate the many benefits, within the liver and extrahepatic, that accompany HCV eradication. Therefore, the panel continues to recommend treatment for all patients with chronic HCV infection, except those with short life expectancies that cannot be remediated by treating HCV, by transplantation, or by other directed therapy. Accordingly, prioritization tables are now less useful and have been removed from this section.

Despite the strong recommendation for treatment for nearly all HCV-infected patients, pretreatment assessment of a patient's understanding of treatment goals and provision of education on adherence and follow-up are essential. A well-established therapeutic relationship between practitioner and patient remains crucial for optimal outcomes with new direct-acting antiviral (DAA) therapies. Additionally, in certain settings there remain factors that impact access to medications and the ability to deliver them to patients. In these settings, practitioners may still need to decide which patients should be treated first. The descriptions below of unique populations may help physicians make more informed treatment decisions for these groups (See Unique Patient Populations: Patients with HIV/HCV Coinfection, Unique Patient Populations: Patients with Decompensated Cirrhosis, Unique Patient Populations: Patients who Develop Recurrent HCV Infection Post-Liver Transplantation, and Unique Patient Populations: Patients with Renal Impairment).

| Goal of Treatment | |
|---|---|
| RECOMMENDED | RATING |
| The goal of treatment of HCV-infected persons is to reduce all-cause mortality and liver-related health adverse consequences, including end-stage liver disease and hepatocellular carcinoma, by the achievement of virologic cure as evidenced by a sustained virologic response. | I, A |

| Recommendation for When and in Whom to Initiate Treatment | |
|---|---|
| RECOMMENDED | RATING |
| Treatment is recommended for all patients with chronic HCV infection, except those with short life expectancies that cannot be remediated by treating HCV, by transplantation, or by other directed therapy. Patients with short life expectancies owing to liver disease should be managed in consultation with an expert. | I, A |

## Clinical Benefit of Cure

The proximate goal of HCV therapy is SVR (virologic cure), defined as the continued absence of detectable HCV RNA at least 12 weeks after completion of therapy. SVR is a marker for cure of HCV infection and has been shown to be durable, in large prospective studies, in more than 99% of patients followed up for 5 years or more (Swain, 2010); (Manns, 2013). Patients in whom an SVR is achieved have HCV antibodies but no longer have detectable HCV RNA in serum, liver tissue, or mononuclear cells, and achieve substantial improvement in liver histology (Marcellin, 1997); (Coppola, 2013); (Garcia-Bengoechea, 1999). Assessment of viral response, including documentation of SVR, requires use of an FDA-approved quantitative or qualitative nucleic acid test (NAT) with a detection level of 25 IU/mL or lower.

Patients who are cured of their HCV infection experience numerous health benefits, including a decrease in liver inflammation as reflected by improved aminotransferase (ie, alanine aminotransferase [ALT], aspartate aminotransferase [AST]) levels and a reduction in the rate of progression of liver fibrosis (Poynard, 2002b). Of 3010 treatment-naive HCV-infected patients with pretreatment and posttreatment biopsies from 4 randomized trials of 10 different IFN-based regimens (biopsies separated by a mean of 20 months), 39% to 73% of patients who achieved an SVR had improvement

in liver fibrosis and necrosis (Poynard, 2002b), and cirrhosis resolved in half of the cases. Portal hypertension, splenomegaly, and other clinical manifestations of advanced liver disease also improved. Among HCV-infected persons, SVR is associated with a more than 70% reduction in the risk of liver cancer (hepatocellular carcinoma [HCC]) and a 90% reduction in the risk of liver-related mortality and liver transplantation (Morgan, 2013); (van der Meer, 2012); (Veldt, 2007).

Cure of HCV infection also reduces symptoms and mortality from severe extrahepatic manifestations, including cryoglobulinemic vasculitis, a condition affecting 10% to 15% of HCV-infected patients (Fabrizi, 2013); (Landau, 2010); (Sise, 2016). HCV-infected persons with non-Hodgkin lymphoma and other lymphoproliferative disorders achieve complete or partial remission in up to 75% of cases following successful therapy for HCV infection (Gisbert, 2005); (Takahashi, 2012); (Svoboda, 2005); (Mazzaro, 2002); (Hermine, 2002). These reductions in disease severity contribute to dramatic reductions in all-cause mortality (van der Meer, 2012); (Backus, 2011). Lastly, patients who achieve SVR have substantially improved qualities of life, which include physical, emotional, and social health (Boscarino, 2015); (Neary, 1999); (Younossi, 2013). Because of the many benefits associated with successful HCV treatment, clinicians should treat HCV-infected patients with antiviral therapy with the goal of achieving an SVR, preferably early in the course of chronic HCV infection before the development of severe liver disease and other complications.

## Benefits of Treatment at Earlier Fibrosis Stages (Metavir Stage Below F2)

Initiating therapy in patients with lower-stage fibrosis augments the benefits of SVR. In a long-term follow-up study, 820 patients with Metavir stage F0 or F1 fibrosis confirmed by biopsy were followed up for up to 20 years (Jezequel, 2015). The 15-year survival rate was statistically significantly better for those who experienced an SVR than for those whose treatment had failed or for those who remained untreated (93%, 82%, and 88%, respectively; $P = .003$). The study results argue for consideration of earlier initiation of treatment. Several modeling studies also suggest a greater mortality benefit if treatment is initiated at fibrosis stages prior to F3 (Øvrehus, 2015); (Zahnd, 2015); (McCombs, 2015).

Treatment delay may decrease the benefit of SVR. In a report of long-term follow-up in France, 820 patients with biopsy-confirmed Metavir stage F0 or F1 fibrosis were followed up for as long as 20 years (Jezequel, 2015). The authors noted rapid progression of fibrosis in 15% of patients during follow-up, and in patients treated successfully, long-term survival was better. Specifically, at 15 years, survival rate was 92% for those with an SVR versus 82% for treatment failures and 88% for those not treated. In a Danish regional registry study, investigators modeled treatment approaches with the aim of evaluating the benefit to the region in terms of reductions in morbidity and mortality and HCV prevalence (Øvrehus, 2015). Although they note that in their situation of low HCV prevalence (0.4%), with approximately 50% undiagnosed, a policy that restricts treatment to those with Metavir fibrosis stage F3 or higher would decrease mortality from HCC and cirrhosis, the number needed to treat to halve the prevalence of the disease is lower if all eligible patients receive treatment at diagnosis. A modeling study based on the Swiss HIV Cohort Study also demonstrated that waiting to treat HCV infection at Metavir fibrosis stages F3 and F4 resulted in 2- and 5-times higher rates of liver-related mortality, respectively, compared with treating at Metavir stage F2 (Zahnd, 2015).

A US Veterans Administration dataset analysis that used very limited end points of virologic response dating from the IFN-treatment era suggested that early (at a Fibrosis-4 [FIB-4] score of <3.25) initiation of therapy increased the benefit attained with respect to likelihood of treatment success and mortality reduction and ultimately decreased the number of patients needed to treat to preserve 1 life by almost 50% (McCombs, 2015).

## Considerations in Specific Populations

Despite the recommendation for treatment of nearly all patients with HCV infection, it remains important for clinicians to understand patient- and disease-related factors that place individuals at risk for HCV-related complications (liver and extrahepatic) as well as for HCV transmission. Although these groups are no longer singled out for high prioritization for treatment, it is nonetheless important that practitioners recognize the unique dimensions of HCV disease and its natural history in these populations. The discussions offered below may assist clinicians in making compelling cases for insurance coverage of treatment when necessary.

## Persons With Advanced Liver Disease

For persons with advanced liver disease (Metavir stage F3 or F4), the risk of developing complications of liver disease such as hepatic decompensation (Child Turcotte Pugh [CTP] Class B or C [Methods Table 3] ) or HCC is substantial and may occur in a relatively short timeframe. A large prospective study of patients with cirrhosis resulting from HCV infection examined the risk of decompensation, including HCC, ascites, jaundice, bleeding, and encephalopathy, and found that the overall annual incidence rate was 3.9% (Sangiovanni, 2006). The National Institutes of Health (NIH)-sponsored HALT–C study included a group of 220 patients with cirrhosis resulting from HCV infection who were observed for approximately 8 years. A primary outcome of death, hepatic decompensation, HCC, or increase in CTP score of 2 or higher occurred at a rate of 7.5% per year (Everson, 2006); (Di Bisceglie, 2008). Patients with a CTP score of 7 or higher experienced a death rate of 10% per year.

Numerous studies have demonstrated that hepatitis C therapy and the achievement of an SVR in this population results in dramatic decreases in hepatic decompensation events, HCC, and liver-related mortality (Morgan, 2013); (van der Meer, 2012); (Backus, 2011); (Dienstag, 2011); (Berenguer, 2009); (Mira, 2013). In the HALT-C study, patients with advanced fibrosis secondary to HCV infection who achieved an SVR, compared with patients with similarly advanced liver fibrosis who did not achieve an SVR, had a decreased need for liver transplantation (hazard ratio [HR], 0.17; 95% confidence interval [CI], 0.06–0.46), decreased development of liver-related morbidity and mortality (HR, 0.15; 95% CI, 0.06–0.38) and decreased HCC (HR, 0.19; 95% CI, 0.04–0.80) (Dienstag, 2011). Importantly, persons with advanced liver disease also require long-term follow-up and HCC surveillance regardless of treatment outcome (see Monitoring Patients Who Are Starting Hepatitis C Treatment, Are on Treatment, or Have Completed Therapy).

Given the clinical complexity and the need for close monitoring, patients with advanced liver disease that has already decompensated (CTP Class B or C [Methods Table 3] ) should be treated by physicians with experience in treating HCV in conjunction with a liver transplantation center if possible (see Unique Patient Populations: Patients with Decompensated Cirrhosis).

## Persons Who Have Undergone Liver Transplantation

In HCV-infected individuals, HCV infection of the liver allograft occurs universally in those with viremia at the time of transplantation. Histologic features of hepatitis develop in about 75% of recipients in the first 6 months following liver transplantation (Neumann, 2004). By the fifth postoperative year, up to 30% of untreated patients have progressed to cirrhosis (Neumann, 2004); (Charlton, 1998). A small proportion of patients (4%-7%) develop an accelerated course of liver injury (cholestatic hepatitis C, associated with very high levels of viremia) with subsequent rapid allograft failure. Recurrence of HCV infection posttransplantation is associated with decreased graft survival for recipients with HCV infection compared to recipients who undergo liver transplantation for other indications (Forman, 2002).

Effective HCV therapy pretransplantation resulting in an SVR (virologic cure) prevents HCV recurrence posttransplantation (Everson, 2003). In addition, complete HCV viral suppression prior to transplantation prevents recurrent HCV infection of the graft in the majority of cases (Forns, 2004); (Everson, 2005). Preliminary data from a study

of patients with complications of cirrhosis secondary to HCV infection, who were wait-listed for liver transplantation, that included patients with MELD scores up to 14 and CTP scores up to 8 found that treatment with sofosbuvir and weight-based ribavirin for up to 48 weeks was well tolerated and was associated with an overall posttransplant SVR rate of 70% (Curry, 2015). Posttransplant SVR was nearly universal among patients who had undetectable HCV RNA for 28 days or longer prior to transplantation.

Treatment of established HCV infection posttransplantation also yields substantial improvements in patient and in graft survival (Berenguer, 2008); (Picciotto, 2007). The availability of effective IFN-free HCV treatments has addressed the major hurdles to treating HCV recurrence posttransplantation: poor tolerability and efficacy. In a multicenter, open-label study that evaluated the ability of sofosbuvir plus ribavirin to induce virologic suppression in 40 patients post-liver transplant with compensated recurrence of HCV infection, daily sofosbuvir and ribavirin for 24 weeks achieved an SVR at 12 weeks (SVR12) in 70% (Charlton, 2015). No deaths, graft losses, or episodes of rejection occurred. Six patients had serious adverse events, all of which were considered unrelated to study treatment. There were no drug interactions reported between sofosbuvir and any of the concomitant immunosuppressive agents. In contrast, treatment with sofosbuvir plus ribavirin with or without PEG-IFN in 64 patients with severe, decompensated cirrhosis resulting from recurrence of HCV infection following liver transplantation was associated with an overall SVR12 rate of 59% and a mortality rate of 13% (Forns, 2015). On an intent-to-treat basis, treatment was associated with clinical improvement in 57% and stable disease in 22% of patients. Given the clinical complexity including drug interactions and the need for close monitoring, patients with liver transplant should be treated by physicians with experience in treating this population (see Unique Patient Populations: Patients Who Develop Recurrent HCV Infection Post-Liver Transplantation).

## Persons at Greater Risk for Rapidly Progressive Fibrosis and Cirrhosis

Fibrosis progression is variable across different patient populations as well as within the same individual over time. Many of the components that determine fibrosis progression and development of cirrhosis in an individual are unknown. However, certain factors, such as coinfection with HIV or hepatitis B virus (HBV) and prevalent coexistent liver diseases (eg, nonalcoholic steatohepatitis [NASH]), are well-recognized contributors to accelerated fibrosis progression.

**HIV coinfection**. HIV coinfection accelerates fibrosis progression among HCV-infected persons, (Benhamou, 1999); (Macias, 2009); (Konerman, 2014) although control of HIV replication and restoration of CD4+ cell counts may mitigate this to some extent (Benhamou, 2001); (Bräu, 2006). However, antiretroviral therapy is not a substitute for HCV treatment. In the largest paired-biopsy study, 282 HIV/HCV-coinfected patients with 435 paired biopsies were prospectively evaluated (Konerman, 2014); one-third of patients showed fibrosis progression of at least one Metavir stage at a median of 2.5 years. Importantly, 45% of patients with no fibrosis on initial biopsy had progression. Finally, a more rapid progression to death following decompensation combined with a lack of widespread access to liver transplantation and poor outcomes following transplantation highlight the need for treatment in this population regardless of current fibrosis stage (see Unique Patient Populations: Patients with HIV/HCV Coinfection (Pineda, 2005); (Merchante, 2006); (Terrault, 2012).

**HBV coinfection and other coexistent liver diseases**. The prevalence of HBV/HCV coinfection is estimated at 1.4% in the United States and 5% to 10% globally (Tyson, 2013); (Chu, 2008). Persons with HBV/HCV coinfection and detectable viremia of both viruses are at increased risk for disease progression, decompensated liver disease, and the development of HCC.

HBV/HCV coinfected individuals are susceptible to a process called viral interference wherein one virus may interfere with the replication of the other virus. Thus, when treating one or both viruses with antiviral drugs, periodic retesting of HBV DNA and HCV RNA levels during and after therapy is prudent, particularly if only one of the viruses is being treated at a time. Treatment of HCV infection in such cases utilizes the same genotype-specific regimens as are recommended for HCV monoinfection (see Initial Treatment of HCV Infection). HBV infections in such cases should be treated as recommended for HBV monoinfection (Lok, 2009).

Persons with other chronic liver diseases who have coincident chronic HCV infection should be considered for hepatitis C therapy, given the potential for rapid progression of liver disease. An IFN-free regimen is generally preferred for immune-mediated liver diseases such as autoimmune hepatitis, because of the potential for IFN-related exacerbation.

## Persons With Extrahepatic Manifestations of Chronic HCV Infection

**Severe renal impairment**. Chronic hepatitis C is associated with a syndrome of cryoglobulinemia and an immune complex and lymphoproliferative disorder that produces arthralgias, fatigue, palpable purpura, renal disease (eg, membranoproliferative glomerulonephritis), neurologic disease (eg, peripheral neuropathy, central nervous system vasculitis), and reduced complement levels (Agnello, 1992). Because patients with chronic hepatitis C frequently have laboratory evidence of cryoglobulins (more than 50% in some series), antiviral treatment is imperative for those with the syndrome of cryoglobulinemia and symptoms or objective evidence of end-organ manifestations. IFN-based regimens can produce clinical remission; however, the adverse effects of IFN may mimic manifestations of cryoglobulinemia (Saadoun, 2014). Although clinical data are not yet available, the use of IFN-free DAA regimens is an attractive option for these patients. Organ-threatening disease (eg, severe neuropathy, renal failure, digital ischemia), in addition to antiviral HCV therapy, should be treated more acutely with immunosuppressive agents or plasmapheresis to clear immune complexes.

Glomerular disease results from deposition of HCV-related immune complexes in the glomeruli (Johnson, 1993). Successful treatment of HCV using IFN-based regimens can reverse proteinuria and nephrotic syndrome but usually does not fully ameliorate azotemia (Johnson, 1994). No clinical trial data are yet available on IFN-free regimens, but the high rates of SVR (virologic cure) with antiviral therapy support their use in management of hepatitis C–related renal disease and cryoglobulinemia.

## Nonhepatic Manifestations of Chronic HCV Infection

The relationship between chronic hepatitis C and diabetes (most notably type 2 diabetes and insulin resistance) is complex and incompletely understood. The prevalence and incidence of diabetes is increased in the context of hepatitis C (White, 2008). In the United States, type 2 diabetes occurs more frequently in HCV-infected patients, with a more than 3-fold greater risk in persons older than 40 years (Mehta, 2000). The positive correlation between quantity of plasma HCV RNA and established markers of insulin resistance confirms this relationship (Yoneda, 2007). Insulin resistance and type 2 diabetes are independent predictors of a more rapid progression of liver fibrosis and an impaired response to IFN-based therapy (Petta, 2008). Patients with type 2 diabetes and insulin resistance are also at increased risk for HCC (Hung, 2010 ).

Successful antiviral treatment has been associated with improved markers of insulin resistance and greatly reduced incidence of new onset of type 2 diabetes and insulin resistance in HCV-infected patients (Arase, 2009). Most recently, antiviral therapy for HCV infection has been shown to improve clinical outcomes related to diabetes. In a large prospective cohort from Taiwan, the incidence rates of end-stage renal disease, ischemic stroke, and acute coronary syndrome were greatly reduced in HCV-infected patients with diabetes who received antiviral therapy compared with untreated, matched controls (Hsu, 2014). Therefore, antiviral therapy may prevent progression to diabetes in patients with prediabetes who have hepatitis C and may reduce renal and cardiovascular complications in patients with established diabetes who have hepatitis C.

In patients with chronic hepatitis C, fatigue is the most frequently reported symptom and has a major effect on quality of life and activity level evidenced by numerous measures of impaired quality of life (Foster, 1998). The presence and severity of fatigue appears to correlate poorly with disease activity, although it may be more common and severe in HCV-infected individuals with cirrhosis (Poynard, 2002a). Despite difficulties in separating fatigue symptoms associated with hepatitis C from those associated with other concurrent conditions (eg, anemia, depression), numerous studies have reported a reduction in fatigue after cure of HCV infection (Bonkovsky, 2007). In the Virahep-C study, 401 patients with HCV infection were evaluated for fatigue prior to and after treatment, using validated scales to assess the presence and severity of fatigue (Sarkar, 2012). At baseline, 52% of patients reported having fatigue, which was more frequent and severe in patients with cirrhosis than in those without cirrhosis. Achieving an SVR was associated with a substantial decrease in frequency and severity of fatigue. A recent analysis of 413 patients from the NEUTRINO and FUSION trials who were treated with a sofosbuvir-containing regimen and who achieved an SVR12 demonstrated improvement in patient fatigue (present in 12%) from the pretreatment level (Younossi, 2014). After achieving an SVR12, participants had marked improvements in fatigue over their pretreatment scores measured by 3 separate validated questionnaires. Additional studies support and extend these findings beyond fatigue, with improvements in overall health-related quality of

life and work productivity observed following successful HCV therapy (Gerber, 2016); (Younossi, 2015b); (Younossi, 2015c); (Younossi, 2015d).

The reported prevalence of HCV infection in patients with porphyria cutanea tarda approximates 50% and occurs disproportionately in those with cirrhosis (Gisbert, 2003). The treatment of choice for active porphyria cutanea tarda is iron reduction by phlebotomy and maintenance of a mildly iron-reduced state without anemia. However, although improvement of porphyria cutanea tarda during HCV treatment with IFN has frequently been described (Takikawa, 1995), there are currently insufficient data to determine whether treating HCV infection with DAAs and achievement of SVR improve porphyria cutanea tarda.

Lichen planus is characterized by pruritic papules involving mucous membranes, hair, and nails. Antibodies to HCV are present in 10% to 40% of patients with lichen planus, but a causal link with chronic infection is not established. Resolution of lichen planus has been reported with IFN-based regimens, but there have also been reports of exacerbation of lichen planus with these treatments. Although it is unknown whether DAAs will have more success against lichen planus, treatment with IFN-free regimens would appear to be a more advisable approach to addressing this disorder (Gumber, 1995).

## Benefit of Treatment to Reduce Transmission

Persons who have successfully achieved an SVR (virologic cure) no longer transmit the virus to others. As such, successful treatment of HCV infection benefits public health. Several health models have shown that even modest increases in successful treatment of HCV infection among persons who inject drugs can decrease prevalence and incidence (Martin, 2013a); (Durier, 2012); (Martin, 2013b); (Hellard, 2012). Models developed to estimate the impact of HCV testing and treatment on the burden of hepatitis C at a country level reveal that large decreases in HCV prevalence and incidence are possible as more persons are successfully treated (Wedemeyer, 2014). There are also benefits to eradicating HCV infection between couples and among families, and thus eliminating the perception that an individual might be contagious. In addition, mother-to-child transmission of HCV does not occur if the woman is not viremic, providing an additional benefit of curing a woman before she becomes pregnant (Thomas, 1998). However, the safety and efficacy of treating women who are already pregnant to prevent transmission to the fetus have not yet been established, and thus treatment is not recommended for pregnant women.

The Society for Healthcare Epidemiology of America (SHEA) advises that health-care workers who have substantial HCV viral replication ($\geq 10^4$ genome equivalents/mL) be restricted from performing procedures that are prone to exposure (Henderson, 2010) and that all health-care workers with confirmed chronic HCV infection should be treated. For reasons already stated above, the achievement of an SVR in such individuals will not only eliminate the risk of HCV transmission to patients but also decrease circumstantial loss of experienced clinicians. Given concerns about underreporting of infection and transmission (Henderson, 2010), the availability of effective, all-oral regimens should lead to greater willingness on the part of exposure-prone clinicians to be tested and treated.

Successful treatment of HCV-infected persons at greatest risk for transmission represents a formidable tool to help stop HCV transmission in those who continue to engage in high-risk behaviors. To guide implementation of hepatitis C treatment as a prevention strategy, studies are needed to define the best candidates for treatment to stop transmission, the additional interventions needed to maximize the benefits of HCV treatment (eg, preventing reinfection), and the cost-effectiveness of the strategies when used in target populations.

Persons who inject drugs. Injection drug use (IDU) is the most common risk factor for HCV infection in the United States and Europe, with an HCV seroprevalence of 10% to 70% (Amon, 2008); (Nelson, 2011); IDU also accounts for the majority of new HCV infections (approximately 70%) and is the key driving force in the perpetuation of the epidemic. Given these facts and the absence of an effective vaccine against HCV, testing and linkage to care combined with treatment of HCV infection with potent IFN-free regimens has the potential to dramatically decrease HCV incidence and prevalence (Martin, 2013b). However, treatment-based strategies to prevent HCV transmission have yet to be studied, including how to integrate hepatitis C treatment with other risk-reduction strategies (eg, opiate substitution therapy, needle and syringe exchange programs) (Martin, 2013a).

In studies of IFN-containing treatments in persons who inject drugs, adherence and efficacy rates are comparable to those of patients who do not use injection drugs. A recent meta-analysis of treatment with PEG-IFN with or without ribavirin in active or recent injection drug users showed SVR rates of 37% and 67% for HCV genotype 1 or 4 and 2 or 3, respectively (Aspinall, 2013). As shorter, better-tolerated, and more efficacious IFN-free therapies are introduced, these SVR rates are expected to improve. Importantly, the rate of reinfection in this population is lower (2.4/100 person-years of observation) than that of incident infection in the general population of injection drug users (6.1-27.2/100 person-years), although reinfection increases with active or ongoing IDU (6.44/100 person-years) and available data on follow-up duration are limited (Aspinall, 2013); (Grady, 2013).

Ideally, treatment of HCV-infected persons who inject drugs should be delivered in a multidisciplinary care setting with services to reduce the risk of reinfection and for management of the common social and psychiatric comorbidities in this population. Regardless of the treatment setting, recent and active IDU should not be seen as an absolute contraindication to HCV therapy. There is strong evidence from various settings in which persons who inject drugs have demonstrated adherence to treatment and low rates of reinfection, countering arguments that have been commonly used to limit access to this patient population (Aspinall, 2013); (Hellard, 2014); (Grebely, 2011). Indeed, combining HCV treatment with needle exchange and opioid agonist therapy programs in this population with a high prevalence of HCV infection has shown great value in decreasing the burden of HCV disease. Elegant modeling studies illustrate the high return on the modest investment of addressing this often-ignored segment of the HCV-infected population (Martin, 2013b). These conclusions were drawn before the introduction of the latest DAA regimens. Conversely, there are no data to support the utility of pretreatment screening for illicit drug or alcohol use in identifying a population more likely to successfully complete HCV therapy. These requirements should be abandoned, because they create barriers to treatment, add unnecessary cost and effort, and potentially exclude populations that are likely to obtain substantial benefit from therapy. Scale up of HCV treatment in persons who inject drugs is necessary to positively impact the HCV epidemic in the United States and globally.

**HIV-infected men who have sex with men (MSM) who engage in high-risk sexual practices**. Over the past decade, a dramatic increase in incident HCV infections among HIV-infected MSM who did not report IDU as a risk factor has been demonstrated in several US cities (van de Laar, 2010). Recognition and treatment of HCV infection (including acute infection) in this population may represent an important step in preventing subsequent infections. As with persons who inject drugs, HIV/HCV-coinfected MSM who engage in ongoing high-risk sexual practices should be treated for their HCV infection in conjunction with continued education on risk-reduction strategies. In particular, safer-sex strategies should be emphasized given the high rates of reinfection after SVR, which may approach 30% over 2 years, in HIV-infected MSM with acute HCV infection (Lambers, 2011).

**Incarcerated persons**. Among incarcerated individuals, the rate of HCV seroprevalence ranges from 30% to 60% (Post, 2013) and the rate of acute infection is approximately 1% (Larney, 2013). Screening for HCV infection is relatively uncommon in state prison systems. Treatment uptake has been limited in part because of the toxic effects and long treatment duration of older IFN-based therapies as well as concerns about cost (Spaulding, 2006). In particular, truncation of HCV treatment owing to release from prison has been cited as a major limitation to widespread, effective HCV treatment in correctional facilities (Post, 2013); (Chew, 2009). Shorter (12- to 24-week) HCV therapies reduce duration of stay-related barriers to HCV treatment in prisons. Likewise, the improved safety of newer, all-oral regimens diminishes concerns of toxic effects. Coordinated treatment efforts within prison systems would likely rapidly decrease the prevalence of HCV infection in this at-risk population, although research is needed in this area.

**Persons on hemodialysis**. The prevalence rate of HCV infection is markedly elevated in persons on hemodialysis and ranged from 2.6% to 22.9% in a large multinational study (Fissell, 2004). Studies in the United States found a similarly elevated prevalence rate of 7.8% to 8.9% (CDC, 2001); (Finelli, 2005). Importantly, the seroprevalence of HCV was found to increase with time on dialysis, suggesting that nosocomial transmission, among other risk factors, plays a role in HCV acquisition in these patients (Fissell, 2004). Improved education and strict adherence to universal precautions can drastically reduce nosocomial HCV transmission risks for persons on hemodialysis (Jadoul, 1998), but clearance of HCV viremia through treatment-induced SVR eliminates the potential for transmission.

HCV-infected persons on hemodialysis have a decreased quality of life and increased mortality compared with uninfected persons on hemodialysis (Fabrizi, 2002); (Fabrizi, 2007); (Fabrizi, 2009). HCV infection in this population also has a deleterious impact on kidney transplantation outcomes with decreased patient and graft survival (Fabrizi, 2014). The

increased risk for nosocomial transmission and the substantial clinical impact of HCV infection in those on hemodialysis are compelling arguments for HCV therapy as effective antiviral regimens that can be used in persons with advanced renal failure become available (see Unique Patient Populations: Patients with Renal Impairment).

## Populations Unlikely to Benefit From HCV Treatment

Patients with a limited life expectancy that cannot be remediated by treating HCV, by transplantation, or by other directed therapy do not require treatment. Patients with short life expectancies owing to liver disease should be managed in consultation with an expert. Chronic hepatitis C is associated with a wide range of comorbid conditions (Butt, 2011); (Louie, 2012). Little evidence exists to support initiation of HCV treatment in patients with limited life expectancy (less than 12 months) owing to non–liver-related comorbid conditions. For these patients, the benefits of HCV treatment are unlikely to be realized and palliative care strategies should take precedence (Holmes, 2006); (Maddison, 2011).

| Recommendation for Pretreatment Assessment | |
|---|---|
| RECOMMENDED | RATING |
| Evaluation for advanced fibrosis using liver biopsy, imaging, and/or noninvasive markers is recommended for all persons with HCV infection, to facilitate an appropriate decision regarding HCV treatment strategy and to determine the need for initiating additional measures for the management of cirrhosis (eg, hepatocellular carcinoma screening) (see HCV Testing and Linkage to Care). | I, A |

An accurate assessment of fibrosis remains vital, as degree of hepatic fibrosis is one of the most robust prognostic factors used to predict HCV disease progression and clinical outcomes (Everhart, 2010). Individuals with severe fibrosis require surveillance monitoring for liver cancer, esophageal varices, and hepatic function (Garcia-Tsao, 2007); (Bruix, 2011). In some instances, the recommended duration of treatment is also longer.

Although liver biopsy is the diagnostic standard, sampling error and observer variability limit test performance, particularly when inadequate sampling occurs. Up to one-third of bilobar biopsies had a difference of at least 1 stage between the lobes (Bedossa, 2003). In addition, the test is invasive and minor complications are common, limiting patient and practitioner acceptance. Serious complications such as bleeding, although rare, are well recognized.

Noninvasive tests to stage the degree of fibrosis in patients with chronic HCV infection include models incorporating indirect serum biomarkers (routine tests), direct serum biomarkers (components of the extracellular matrix produced by activated hepatic stellate cells), and vibration-controlled transient liver elastography. No single method is recognized to have high accuracy alone and each test must be interpreted carefully. A recent publication of the Agency for Healthcare Research and Quality found evidence in support of a number of blood tests; however, at best, they are only moderately useful for identifying clinically significant fibrosis or cirrhosis (Selph, 2014).

Vibration-controlled transient liver elastography is a noninvasive way to measure liver stiffness and correlates well with measurement of substantial fibrosis or cirrhosis in patients with chronic HCV infection. The measurement range does overlap between stages (Ziol, 2005); (Afdhal, 2015); (Castera, 2005).

The most efficient approach to fibrosis assessment is to combine direct biomarkers and vibration-controlled transient liver elastography (Boursier, 2012); (European Association for the Study of the Liver and Asociacion Latinoamericana para el Estudio del Higado, 2015). A biopsy should be considered for any patient who has discordant results between the 2 modalities that would affect clinical decision making. For example, one shows cirrhosis and the other does not. The need for liver biopsy with this approach is markedly reduced.

Alternatively, if direct biomarkers or vibration-controlled transient liver elastography are not available, the AST-to-platelet ratio index (APRI) or FIB-4 index score can help (Sebastiani, 2009); (Castera, 2010); (Chou, 2013), although neither test is sensitive enough to rule out substantial fibrosis (Chou, 2013). Biopsy should be considered in those in whom more accurate fibrosis staging would impact treatment decisions. Individuals with clinically evident cirrhosis do not require additional staging (biopsy or noninvasive assessment).

| Recommendation for Repeat Liver Disease Assessment | |
|---|---|
| RECOMMENDED | RATING |
| Ongoing assessment of liver disease is recommended for persons in whom therapy is deferred. | I, C |

When therapy is deferred, it is especially important to monitor liver disease in these patients. In line with evidence-driven recommendations for treatment of nearly all HCV-infected patients, several factors must be taken into consideration if treatment deferral is entertained or mandated by lack of medication access. As noted, strong and accumulating evidence argue against deferral because of decreased all-cause morbidity and mortality, prevention of onward transmission, and quality-of-life improvements for patients treated regardless of baseline fibrosis. Additionally, treatment of HCV infection may improve or prevent extraheptatic complications, including diabetes mellitus, cardiovascular disease, renal disease, and B-cell non-Hodgkin lymphoma (Conjeevaram, 2011); (Hsu, 2015); (Torres, 2015), which are not tied to fibrosis stage (Allison, 2015); (Petta, 2016). Deferral practices based on fibrosis stage alone are inadequate and shortsighted.

Fibrosis progression varies markedly between individuals based on host, environmental, and viral factors (Table 1); (Feld, 2006). Fibrosis may not progress linearly. Some individuals (often those aged >50 years) may progress slowly for many years followed by an acceleration of fibrosis progression. Others may never develop substantial liver fibrosis despite longstanding infection. The presence of existing fibrosis is a strong risk factor for future fibrosis progression. Fibrosis results from chronic hepatic necroinflammation, and thus a higher activity grade on liver biopsy and higher serum transaminase values are associated with more rapid fibrosis progression (Ghany, 2003). However, even patients with normal ALT levels may develop substantial liver fibrosis over time (Pradat, 2002); (Nutt, 2000). The limitations of transient elastography and liver biopsy in ascertaining the progression of fibrosis must be recognized.

Host factors associated with more rapid fibrosis progression include male sex, longer duration of infection, and older age at the time of infection (Poynard, 2001). Many patients have concomitant nonalcoholic fatty liver disease, and the presence of hepatic steatosis with or without steatohepatitis on liver biopsy, elevated body mass index, insulin resistance, and iron overload are associated with fibrosis progression (Konerman, 2014); (Everhart, 2009). Chronic alcohol use is an important risk factor because alcohol consumption has been associated with more rapid fibrosis progression (Feld, 2006). A safe amount of alcohol consumption has not been established. Cigarette smoking may also lead to more rapid fibrosis progression. For more counseling recommendations, please see Testing and Linkage to Care.

Immunosuppression leads to more rapid fibrosis progression, particularly HIV/HCV coinfection and solid organ transplantation (Macias, 2009); (Konerman, 2014); (Berenguer, 2013). Therefore, immunocompromised patients should be treated even if they have mild liver fibrosis at presentation.

Level of HCV RNA does not correlate with stage of disease (degree of inflammation or fibrosis). Available data suggest that fibrosis progression occurs most rapidly in patients with HCV genotype 3 infection (Kanwal, 2014); (Bochud, 2009). Aside from coinfection with HBV or HIV, no other viral factors are consistently associated with disease progression.

Although an ideal interval for assessment has not been established, annual evaluation is appropriate to discuss modifiable risk factors and to update testing for hepatic function and markers for disease progression. For all individuals with advanced fibrosis, liver cancer screening dictates a minimum of evaluation every 6 months.

| When and in Whom to Initiate HCV Therapy Table 1. Factors Associated with Accelerated Fibrosis Progression | |
|---|---|
| HOST | VIRAL |
| **Nonmodifiable**<br>• Fibrosis stage<br>• Inflammation grade<br>• Older age at time of infection<br>• Male sex<br>• Organ transplant<br>**Modifiable**<br>• Alcohol consumption<br>• Nonalcoholic fatty liver disease<br>• Obesity<br>• Insulin resistance | • HCV genotype 3<br>• Coinfection with hepatitis B virus or HIV |

**Last update:** July 6, 2016

# Overview of Cost, Reimbursement, and Cost-effectiveness Considerations for Hepatitis C Treatment Regimens

The Hepatitis C Guidance describes how to diagnose, link to care, and treat most groups of patients with HCV (AASLD-IDSA, 2016). However, a common challenge is reduced access to treatment caused by restrictions on drug reimbursement. This section summarizes the US payer system, explains the concepts of cost, price, cost-effectiveness, value, and affordability, and reviews current evidence of the cost-effectiveness of strategies to improve access to treatment. Although these may sound similar and are often confused, the following discussion will seek to clarify these terms with regard to HCV therapy. To be clear, this section is informational. As explained below, actual costs are rarely known. Accordingly, the HCV Guidance does not utilize cost-effectiveness analysis to guide recommendations at this time.

| Table. Abbreviations Specific to Overview of Cost, Reimbursement, and Cost-Effectiveness Considerations for Hepatitis C Treatment Regimens | |
|---|---|
| Abbreviation | Expanded Name |
| ACA | Affordable Care Act |
| AMP | Average manufacturer price |
| AWP | Average wholesale price[a] |
| CEA | Cost-effectiveness analysis |

| Table. Abbreviations Specific to Overview of Cost, Reimbursement, and Cost-Effectiveness Considerations for Hepatitis C Treatment Regimens | |
|---|---|
| Cn | Cost of new therapy |
| Co | Cost of old therapy |
| ICER | Incremental cost-effectiveness ratio |
| PBM | Pharmacy benefit manager |
| QALY | Quality-adjusted life-year |
| QALYn | Quality-adjusted life-year of new therapy |
| QALYo | Quality-adjusted life-year of old therapy |
| WAC | Wholesale acquisition cost[b] |
| a. "List price" for wholesale pharmacies to purchase drugs.<br>b. Typically, approximately 17% off of AWP. | |

## Drug Cost and Reimbursement

There are many organizations involved with the distribution of hepatitis C drugs and each can impact costs, as well as the decision of which regimens are reimbursed (US GAO, 2015); (US CBO, 2015). The roles these organizations have in determining the actual price paid for drugs and who has access to treatment include the following:

- Pharmaceutical companies determine the wholesale acquisition cost (WAC) of a drug (like a “sticker price”). The company negotiates contracts with other organizations within the pharmaceutical supply chain that allow for rebates or discounts that decrease the actual price paid.
- Pharmacy benefit managers (PBMs) often negotiate contracts with pharmaceutical companies on behalf of health insurance companies. Such contracts may include restrictions on who can be reimbursed for treatment and may offer exclusivity (restrictions on which medications can be prescribed) in exchange for lower prices, often provided in the form of WAC discounts.
- Private insurance companies often have separate pharmacy and medical budgets and use PBMs or negotiate drug pricing directly with pharmaceutical companies. Insurance companies determine formulary placement, which impacts choice of regimens and out-of-pocket expenses for patients. An insurance company can cover private, managed care Medicaid, and Medicare plans and can have different formularies for each line of business.
- Medicaid is a heterogeneous compilation of insurance plans that includes fee-for-service and managed care options. Most plans negotiate rebates with pharmaceutical manufacturers (through PBMs or individually). Differences in negotiated contracts between plans have led to Medicaid patients in different states having widely varied access to HCV therapy (Canary, 2015). Disparities may even exist between patients enrolled in different Medicaid plans within the same state (Barua, 2015). State Medicaid programs have benefited from the Patient Protection and Affordable Care Act (ACA), although such benefits are mitigated in states that have opted out of expanding Medicaid coverage under the ACA. In general, for single-source drugs such as the currently available hepatitis C treatments, Medicaid plans receive the lowest price offered to any other payer (outside certain government agencies), and the minimum Medicaid drug rebate is 23.1% of the average manufacturer price (AMP; another payment benchmark).
- Medicare covers HCV drugs through Part D benefits and is prohibited by law from directly negotiating drug prices. These drug plans are offered through PBMs or commercial health plans, which may negotiate discounts or rebates with pharmaceutical companies.
- The Veterans Health Administration receives mandated rebates through the Federal Supply Schedule, which sets drug prices for a number of government agencies, including the Department of Veterans Affairs, federal prisons, and the Department of Defense, and typically receives substantial discounts over average wholesale price (AWP;

another payment benchmark).
- State prisons and jails are usually excluded from Medicaid-related rebates and often do not have the negotiating leverage of larger organizations and may end up paying higher prices than most other organizations.
- Specialty pharmacies receive dispensing fees and may receive additional payments from contracted insurance companies, PBMs, or pharmaceutical companies to provide services such as adherence support, management of adverse effects, and outcomes measurements such as early discontinuation rates and sustained virologic response rates.
- Patients incur costs (eg, copayment or coinsurance) determined by their pharmacy plan. Patient assistance programs through pharmaceutical companies or foundations can cover many of these out-of-pocket expenses or provide drugs at no cost to qualified patients who are unable to pay.

With the exception of mandated rebates, negotiations of drug prices are considered confidential business contracts and, therefore, there is almost no transparency regarding the actual prices paid for hepatitis C drugs (Saag, 2015). However, the average negotiated discount of 22% in 2014 increased to 46% off the WAC in 2015, implying that many payers are paying well below the WAC price for HCV regimens (US Senate Committee on Finance, 2016).

## Cost-effectiveness

Cost-effectiveness analysis (CEA) compares the relative costs and outcomes of two or more interventions. CEA explicitly recognizes budget limitations for healthcare spending and seeks to maximize public health benefits within those budget constraints. CEA is typically expressed as an incremental cost-effectiveness ratio (ICER), the ratio of change in costs between two or more interventions to the change in effects. In short, CEA provides a framework for comparing the healthcare costs and societal benefits of different technologies or therapies.

To make such comparisons, three questions first need to be answered:

1. **How much more will we spend on a new intervention?** This is not as simple as determining the cost of a new medication, but also the cost of the intervention over the course of a person's lifetime and the cost savings from the prevention or attenuation of disease complications. Further, the cost of current standard therapy and the cost of the disease should be considered, so incremental cost-effectiveness requires understanding the incremental cost of new versus old. Given the lack of transparency in healthcare costs in the United States, this is at best an inexact estimate.

2. **How much more benefit accrues from a new intervention?** To compare health interventions using a single metric across diseases and interventions and to integrate both duration and quality of life gained, benefit is measured in terms of quality-adjusted life-years (QALYs). CEA asks: "If a new therapy is implemented, how many more QALYs will likely be gained from the new medications?"

3. **How much is society willing to pay to gain one additional QALY?** This willingness-to-pay threshold typically varies by country and acknowledges opportunity costs. Spending more money on one disease may mean spending less money on other diseases. Similarly, spending more on health care means less spending for education, defense, or environment. Although it may seem inappropriate to set a monetary value on human life, willingness-to-pay thresholds only acknowledge that budgets are finite and provide a measure of societal value. They are not intended to be a moral valuation.

Once these questions are answered, CEA provides a simple rubric for making normative determinations about whether a new technology provides good value for its cost. First, the ICER of the new therapy is calculated as: (Cn – Co) ÷ (QALYn – QALYo), where Cn is the cost of the new therapy, Co is the cost of the old (comparison) therapy, and QALY is quality-adjusted life-year, shown as new (n) or old (o).

Once the ICER is determined, it is compared with the societal willingness-to-pay threshold (typically considered to be

$50,000 to $100,000/QALY gained in the United States). ICERs that are less than the willingness-to-pay threshold represent a good value, and such interventions can be considered cost effective. Interventions with ICERs exceeding the willingness-to-pay threshold would be less efficient uses of limited budget resources.

## Affordability

An intervention that is cost effective is not necessarily affordable. Affordability refers to whether a payer has sufficient resources in its annual budget to pay for a new therapy for all who might need or want it within that year. Several characteristics of CEA limit its ability to speak to the budget impact of interventions being implemented in the real world:

1. **Perspective on cost**: CEA seeks to inform decisions about how society should prioritize healthcare spending. As such, it typically assumes a societal perspective on costs and includes all costs from all payers, including out-of-pocket expenses for the patient. When making coverage decisions for therapy, however, an insurer considers only its own revenues and expenses.

2. **Time horizon**: CEA uses a lifetime time horizon, meaning that it considers lifetime costs and benefits, including those that occur in the distant future. Business budget planning, however, typically assumes a 1-year to 5-year perspective. Savings that may accrue 30 years from now have very little impact on spending decisions today, because they have little bearing on the solvency of the budget today.

3. **Weak association between willingness to pay and the real-world bottom line**: Societal willingness-to-pay thresholds in CEAs are not based on actual budget calculations and have little connection to a payer's bottom line. Given the rapid development of new technologies, funding all of them, even if they all fell below the societal willingness-to-pay threshold, would likely lead to uncontrolled growth in demand and would likely exceed the limited healthcare budget.

There is no mathematic formula that provides a good means of integrating the concerns of value and affordability. When new therapies for HCV are deemed cost effective, it indicates that such therapies provide excellent benefits for the resources invested in their use and that providing more therapy is a good investment in the long term. Determining the total resources that can be spent on HCV treatment, however, depends on political and economic factors that are not captured by cost-effectiveness determinations.

## Cost-effectiveness of Current All-Oral Regimens for Hepatitis C Treatment

Recently published studies compared all-oral, direct-acting antiviral (DAA) regimens to previous standard-of-care regimens (usually IFN based) to calculate ICERs. In general, treating patients with more advanced fibrosis or cirrhosis provided better value (lower ICERs) than treating those with milder disease. Indeed, the ICERs of therapy for treatment-naive patients who do not have cirrhosis are generally within the range of other widely used medical therapies. Although it is possible to make some general comments about cost-effectiveness for these new HCV drug regimens, it is important to recognize that this task is difficult, owing to the rapid changes in available drugs, the variability in cost (see above), and individual patient characteristics such as fibrosis stage, comorbidities, estimated life expectancy, and HCV genotype.

## HCV Genotype 1

There are several cost-effectiveness studies of IFN-free, DAA therapy for HCV genotype 1 infection across various models that use independently derived assumptions about disease progression, costs, and quality of life. Most have shown ICERs within the range of other accepted medical practices. Published ICERs of all-oral regimens for treatment-naive patients with HCV genotype 1 infection in the United States range from cost saving (less than $0) to $31,452 per QALY gained, depending on the presence or absence of cirrhosis (Chatwal, 2015); (Najafzadeh, 2015); (Linas, 2015); (Younossi, 2015a); (Tice, 2015); (Chidi, 2016). However, ICERs as high as $84,744 to $178,295 per QALY gained have been reported among the more recalcitrant IFN-experienced patients with fibrosis who are being retreated using an IFN-

free regimen (Chatwal, 2015).

### HCV Genotype 2

ICERs of all-oral regimens in HCV genotype 2–infected persons ranged from $35,500 to $238,000 per QALY gained, depending on the presence or absence of cirrhosis (Chatwal, 2015); (Najafzadeh, 2015); (Linas, 2015). In analyses among treatment-naive patients without cirrhosis, the AWP of sofosbuvir led to ICERs being higher than US willingness-to-pay thresholds, but with the lower costs negotiated by some payers, the ICERs for all patient groups would fall within accepted pay thresholds for other accepted medical interventions in the United States (Najafzadeh, 2015); (Linas, 2015).

### HCV Genotype 3

The ICERs of IFN-free therapy for HCV genotype 3 infection reflect the clinical reality that IFN-free regimens are less effective for treating patients with this genotype than any other genotype. As a result, ICERs of all-oral regimens ranged from being inferior (costing more with lower effectiveness) to $410,548 per QALY gained, depending on the presence or absence of cirrhosis (Chatwal, 2015); (Linas, 2015). In one analysis, the preferred therapy for HCV genotype 3 infection from a purely cost-effectiveness–based perspective was PEG-IFN, ribavirin, and sofosbuvir (Linas, 2015).

### HCV Genotype 4

For HCV genotype 4 infection, ICERs of all-oral regimens ranged from $34,349 to $80,793 per QALY gained, depending on the presence or absence of cirrhosis (Chatwal, 2015). However, these findings are based on treatment efficacy from small studies and must be confirmed once better data on treatment response are available.

### Limitations

These published CEAs considered a variety of all-oral and nonoral regimens, often for different treatment durations, and patient populations and were not always consistent with current treatment recommendations and guidelines. Some regimens recommended in the HCV Guidance have not yet been subjected to economic analyses. Analyses used published WAC prices, which are lower than AWP prices used in older CEAs but higher than the actual prices paid by many payers and reflect an upper threshold of ICER, but most also examined the impact of negotiated price discounts on cost-effectiveness conclusions. Other analyses that are not described here include, for example, the impact of immediate versus delayed treatment (Rein, 2015); (Chahal, 2016); (Martin, 2016) and HCV treatment as prevention (Harris, 2016); (He, 2016); (Martin, 2016).

### Conclusions

Although the wholesale acquisition costs of HCV drugs often make treatment appear unaffordable, the reality is that insurers, PBMs, and government agencies negotiate pricing and few actually pay the much-publicized WAC (retail). However, the negotiated pricing and cost structure for pharmaceutical products in the United States are not transparent, and it is therefore difficult to estimate the true cost and cost-effectiveness of HCV drugs. Whatever the actual current cost of HCV DAAs, competition and negotiated pricing have not improved access to care for many persons with HCV infection and continue to limit the public health impact of these new therapies. Insurers, government, and pharmaceutical companies should work together to bring medication prices to the point where all of those in need of treatment are able to afford and readily access it.

**Last update:** July 6, 2016

## Monitoring Patients Who Are Starting HCV Treatment, Are on

# Treatment, or Have Completed Therapy

This section provides guidance on monitoring patients with chronic hepatitis C who are starting treatment, are on treatment, or have completed treatment. The section is divided into three parts: pretreatment and on-treatment monitoring, posttreatment follow-up for persons in whom treatment has failed to clear virus, and posttreatment follow-up for those who achieved a sustained virologic response (SVR; virologic cure).

## Recommended Assessments Prior to Starting Antiviral Therapy

| RECOMMENDED | RATING |
|---|---|
| • Staging of hepatic fibrosis is essential prior to HCV treatment (see Testing and Linkage to Care and see When and in Whom to Treat).<br>• Assessment of potential drug-drug interactions with concomitant medications is recommended prior to starting antiviral therapy.<br>  ◦ Patients should also be educated on the proper administration of medications (eg, dose, frequency of medicines, food effect, missed doses, adverse effects, etc), the crucial importance of adherence, and the necessity for close supervision and blood tests during and after treatment.<br><br>**The following laboratory tests are recommended within 12 weeks prior to starting antiviral therapy:**<br><br>• Complete blood count (CBC); international normalized ratio (INR)<br>• Hepatic function panel (albumin, total and direct bilirubin, alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase levels)<br>• Calculated glomerular filtration rate (GFR)<br>• Thyroid-stimulating hormone (TSH) if IFN is used<br><br>**The following laboratory testing is recommended at any time prior to starting antiviral therapy:**<br><br>• HCV genotype and subtype<br>• Quantitative HCV RNA (HCV viral load) | I, C |
| Patients scheduled to receive an HCV NS3 protease inhibitor (paritaprevir, simeprevir, grazoprevir) should be assessed for a history of decompensated liver disease and for severity of liver disease using CTP score. Patients with current or prior history of decompensated liver disease or with a current CTP score of 7 or greater should NOT receive treatment with regimens that contain NS3 protease inhibitors due to increased area under the curve (AUC) and/or lack of safety data. Similarly, patients with a CTP score of 5 or 6, who cannot be closely monitored for laboratory or clinical symptoms during treatment, should not receive treatment with a regimen that contains paritaprevir/ritonavir. | I, A |
| All patients initiating HCV DAA therapy should be assessed for HBV coinfection with HBsAg, anti-HBs, and anti-HBc. | IIa, B |
| Testing for the presence of resistance-associated substitutions (RASs) prior to starting treatment should be performed as recommended in the Initial Treatment and the Retreatment Sections. | IIb, B |

**Table: NS5A Resistance-Associated Substitutions (RASs) with Potential for Clinical Significance**

| Wild-type Amino Acid (sensitive) | Position | Substitution Amino Acid |
|---|---|---|
| M | 28 | A/G/T |
| Q | 30 | D/E/H/G/K/L/R |
| L | 31 | F/M/V |
| Y | 93 | C/H/N/S |

The role of NS5A resistance-associated substitutions (RASs) is emerging. NS5A RASs appear to have impact on treatment response with regimens that include an NS5A inhibitor and this impact occurs primarily with genotype 1a and genotype 3 infections. However, the magnitude of the impact on treatment response varies with the specific combination of direct-acting antivirals. Recommendations on the need for NS5A testing, particularly at baseline prior to exposure to a NS5A inhibitor, will be made for individual regimens where there is sufficient data and it is felt the impact is great enough to be clinically significant and warrant testing. This is a rapidly evolving part of the field and will be updated regularly to reflect new and emerging data.

## Pretreatment and On-Treatment Monitoring

The pretreatment testing described here assumes that a decision to treat with antiviral medications has already been made and that the testing involved in deciding to treat, including testing for HCV genotype and assessment of hepatic fibrosis, has already been completed (see When and in Whom to Initiate HCV Therapy).

Prior to starting treatment, patients should be evaluated for potential drug-drug interactions with selected antiviral medications (eg, http://www.hep-druginteractions.org).

## Table: Drug Interactions with Direct-Acting Antivirals and Selected Concomitant Medications

**( x = assess potential drug interaction. Hover over column labels for complete treatment name.)**

| Concomitant Medications | DCV | LDV | PrOD | SMV | SOF | EBV/GRZ | VEL |
|---|---|---|---|---|---|---|---|
| Acid-reducing agents* | | X | X | | | | X |
| Alfuzosin/tamsulosin | | | X | | | | |
| Amiodarone | X | X | X | X | X | | X |
| Anticonvulsants* | X | X | X | X | X | X | X |
| Antiretrovirals* | **See HIV section** | | | | | | |
| Azole antifungals* | X** | | X | X | | X | |
| Buprenorphine/naloxone | | | X | | | | |
| Calcineurin inhibitors* | | | X | X | | X | |
| Calcium channel blockers* | X | | X | X | | X | |
| Cisapride | | | X | X | | X | |
| Digoxin | X | X | | X | | X | |
| Ergot derivatives | | | X | | | | |
| Ethinyl estradiol–containing products | | | X | | | | |
| Furosemide | | | X | | | | |
| Gemfibrozil | | | X | | | | |
| Glucocorticoids* | X | | X (inhaled, intranasal) | X | | X | |
| Herbals<br>St. John's wort<br>Milk thistle | X | X | X | X<br>X | X | X<br>X | X |
| HMG-CoA reductase inhibitors (statins)* | X | X | X | X | | X | |
| Macrolide antimicrobials* | X** | | | X | | X | |
| Other antiarrythmics* | | | X | X | | X | |
| Phosphodiesterase inhibitors* | | | X | X | | X | |
| Pimozide | | | X | | | | |
| Rifamycin antimicrobials* | X | X | X | X | X | X | X |
| Salmeterol | | | X | | | | |
| Sedatives* | | | X | X | | X | |

* Some drug interactions are not class specific; see product prescribing information for specific drugs within a class.
** Requires a daclatasvir dose modification

## Recommended Monitoring During Antiviral Therapy

| RECOMMENDED | RATING |
|---|---|
| Clinic visits or telephone contact are recommended as clinically indicated during treatment to ensure medication adherence and to monitor for adverse events and potential drug-drug interactions with newly prescribed medications. | I, B |
| Complete blood count (CBC), creatinine level, calculated glomerular filtration rate (GFR), and hepatic function panel are recommended after 4 weeks of treatment and as clinically indicated. Thyroid-stimulating hormone (TSH) is recommended every 12 weeks for patients receiving IFN. More frequent assessment for drug-related toxic effects (eg, CBC for patients receiving ribavirin) is recommended as clinically indicated. Patients receiving elbasvir/grazoprevir should be monitored with hepatic function panel at 8 weeks (and again at 12 weeks if receiving 16 weeks of treatment). | I, B |
| A 10-fold increase in alanine aminotransferase (ALT) activity at week 4 should prompt discontinuation of therapy. Any increase in ALT of less than 10-fold at week 4 and accompanied by any weakness, nausea, vomiting, jaundice, or significantly increased bilirubin, alkaline phosphatase, or international normalized ratio, should also prompt discontinuation of therapy. Asymptomatic increases in ALT of less than 10-fold elevated at week 4 should be closely monitored and repeated at week 6 and week 8. If levels remain persistently elevated, consideration should be given to discontinuation of therapy. | I, B |
| Quantitative HCV viral load testing is recommended after 4 weeks of therapy and at 12 weeks following completion of therapy. Antiviral drug therapy should NOT be interrupted or discontinued if HCV RNA levels are not performed or available during treatment. | I, B |
| Quantitative HCV viral load testing can be considered at the end of treatment and 24 weeks or longer following the completion of therapy. | I, B |
| Patients with compensated cirrhosis‡ who are receiving paritaprevir/ritonavir-based regimens should be assessed for clinical signs of decompensated liver disease (eg, ascites, encephalopathy) and for biochemical evidence of liver injury with a hepatic function panel at week 2 and week 4 of treatment, and as needed during the remainder of treatment. Paritaprevir/ritonavir-based regimens should be discontinued if patients develop ascites or encephalopathy or a significant increase in direct bilirubin or ALT or AST. | I, A |
| For HBsAg+ patients who are not already on HBV suppressive therapy, monitoring of HBV DNA levels during and immediately after DAA therapy for HCV is recommended and antiviral treatment for HBV should be given if treatment criteria for HBV are met. | IIa, B |

‡ For decompensated cirrhosis, please refer to the appropriate section.

## Recommendations for Discontinuation of Treatment Because of Lack of Efficacy

| RECOMMENDED | RATING |
|---|---|
| If HCV RNA is detectable at week 4 of treatment, repeat quantitative HCV RNA viral load testing is recommended after 2 additional weeks of treatment (treatment week 6). If quantitative HCV viral load has increased by greater than 10-fold (>1 $\log_{10}$ IU/mL) on repeat testing at week 6 (or thereafter), then discontinuation of HCV treatment is recommended. | III, C |
| The significance of a positive HCV RNA test result at week 4 that remains positive, but lower, at week 6 or week 8 is unknown. No recommendation to stop therapy or extend therapy can be provided at this time. | III, C |

## Recommended Monitoring for Pregnancy-related Issues Prior to and During Antiviral Therapy that Includes Ribavirin

| RECOMMENDED | RATING |
|---|---|
| Women of childbearing age should be counseled not to become pregnant while receiving ribavirin-containing antiviral regimens, and for up to 6 months after stopping. | I, C |
| Male partners of women of childbearing age should be cautioned to prevent pregnancy while they are receiving ribavirin-containing antiviral regimens, and for up to 6 months after stopping. | I, C |
| Serum pregnancy testing is recommended for women of childbearing age prior to beginning treatment with a regimen that includes ribavirin. | I, C |
| Since the safety of DAA regimens that do not include ribavirin has not been established during pregnancy, counseling and serum pregnancy testing should be offered to women of childbearing age before beginning HCV treatment. | I, C |
| Assessment of contraceptive use and of possible pregnancy is recommended at appropriate intervals during (and for 6 months after) ribavirin treatment for women of childbearing potential, and for female partners of men who receive ribavirin treatment. | I, C |

During treatment, individuals should be followed up at clinically appropriate intervals to ensure medication adherence, assess adverse events and potential drug-drug interactions, and monitor blood test results necessary for patient safety. Frequency and type of contact (eg, clinic visit, phone call, etc) are variable, but need to be sufficient to assess patient safety and response to treatment, as outlined above.

The assessment of HCV viral load at week 4 of therapy is useful to determine initial response to therapy and adherence. In phase III clinical trials, almost all patients who did not have cirrhosis had undetectable HCV RNA level at week 4; those with cirrhosis may require more than 4 weeks of treatment before HCV RNA level is undetectable. There are minimal data on how to use HCV RNA level during treatment to determine when to stop treatment for futility. The current recommendation to repeat quantitative HCV RNA testing at week 4 of treatment and to discontinue treatment if the quantitative HCV RNA level increases by more than 10-fold (>1 $\log_{10}$ IU/mL) is based on expert opinion. There are no data to support stopping treatment based on detectable HCV RNA results at weeks 2, 3, or 4 of treatment, or that detectable HCV RNA level at these time points signifies medication nonadherence. Although HCV RNA testing is recommended at

week 4 of treatment, the absence of an HCV RNA level at week 4 is not a reason to discontinue treatment. Quantitative HCV RNA level testing at the end of treatment will help to differentiate viral breakthrough from relapse, if necessary. Some may choose to forego end-of-treatment viral load testing, given the high rates of viral response with the newer regimens, and to focus on the week 12 posttreatment viral load. Virologic relapse is rare at 12 or more weeks after completing treatment. Nevertheless, repeat quantitative HCV RNA testing can be considered at 24 or more weeks after discontinuing treatment for selected patients.

During clinical trials with ELB/GRZ with or without ribavirin, 1% of subjects experienced elevations of ALT from normal levels to greater than 5 times the upper limit of normal (ULN), generally at or after treatment week 8. ALT elevations were typically asymptomatic and most resolved with ongoing therapy or completion of therapy. Higher rates of late ALT elevations occurred in females, Asians, and those 65 years or older. Hepatic laboratory testing should be performed prior to therapy, at treatment week 8, and as clinically indicated. For patients receiving 16 weeks of therapy, additional hepatic laboratory testing should be performed at treatment week 12 (elbasvir and grazoprevir package insert). Patients who have compensated cirrhosis (Child's A) and are receiving paritaprevir/ritonavir-based regimens should be followed closely. (Please see above and statement on FDA warning regarding the use of PrOD or PrO in patients with cirrhosis.)

Patients who are being treated with amiodarone should not receive sofosbuvir-based regimens due to risk of life-threatening arrhythmias.

## Pregnancy

Ribavirin causes fetal death and fetal abnormalities in animals and thus it is imperative for persons of childbearing potential who receive the drug to use at least two reliable forms of effective contraception during treatment and for a period of 6 months thereafter. Ethinyl estradiol-containing contraceptives should be avoided in those receiving paritaprevir/ritonavir/ombitasvir plus dasabuvir due to risk of developing elevated transaminases. It is recommended that the healthcare practitioner document the discussion of potential teratogenic effects of ribavirin in the patient's medical record. Sofosbuvir, ledipasvir, paritaprevir, ombitasvir, and dasabuvir are pregnancy category B, although there are limited data on the use of these drugs in pregnancy. It is recommended that female patients have a thorough discussion of potential pregnancy-related drug effects prior to starting antiviral treatment. Given the relatively short duration of treatment and the potential to use ribavirin-free regimens in many patients, the potential risks and benefits of delaying pregnancy until HCV antiviral treatment is completed should be considered. The education of patients and caregivers about potential adverse effects and their management is an integral component of treatment and is important for a successful outcome in all patient populations.

## Reactivation of HBV

Cases of HBV reactivation, occasionally fulminant, during or after DAA therapy have been reported in HBV/HCV coinfected patients who were not already on HBV suppressive therapy (Hayashi, 2016); (Takayama, 2016); (Ende, 2015); (Collins, 2015); (De Monte, 2016); (Sulkowski, 2016); (Wang, 2016). In light of these observations, and consistent with general recommendations for the assessment of the HCV-infected patient, all patients initiating HCV DAA therapy should be assessed for HBV coinfection with testing for HBsAg, anti-HBs, and anti-HBc. HBV vaccination is recommended for all susceptible individuals. A test for HBV DNA should be obtained prior to DAA therapy in patients who are HBsAg positive. Patients meeting criteria for treatment of active HBV infection should be started on therapy at the same time (or before) HCV DAA therapy is initiated (AASLD Guidelines for Treatment of Chronic Hepatitis B). Patients with low or undetectable HBV DNA levels should be monitored at regular intervals (usually not more frequently than every 4 weeks) for HBV reactivation with HBV DNA, and those patients with HBV DNA levels meeting treatment criteria should initiate HBV therapy (AASLD Guidelines for Treatment of Chronic Hepatitis B). There are insufficient data to provide clear recommendations for the monitoring of patients testing positive either for anti-HBc alone (isolated anti-HBc) or for anti-HBs and anti-HBc (immune recovery). However, the possibility of HBV reactivation should be considered in these groups in the event of unexplained increases in liver enzymes during and/or after completion of DAA therapy.

## Monitoring Patients Who Have Completed Treatment

Patients who do not achieve an SVR, because of failure of the treatment to clear, or to maintain clearance of HCV infection with relapse after treatment completion, have ongoing HCV infection and the possibility of continued liver injury and transmission. Such patients should be monitored for progressive liver disease and considered for retreatment when alternative treatments are available. Patients who have undetectable HCV RNA in the serum, when assessed by a sensitive polymerase chain reaction (PCR) assay, 12 or more weeks after completing treatment, are deemed to have achieved an SVR. In these patients, HCV-related liver injury stops, although the patients remain at risk for non-HCV-related liver disease, such as fatty liver disease or alcoholic liver disease. Patients with cirrhosis remain at risk for developing hepatocellular carcinoma.

### Recommended Monitoring for Patients in Whom Treatment Failed to Achieve a Sustained Virologic Response

| RECOMMENDED | RATING |
|---|---|
| Disease progression assessment every 6 months to 12 months with a hepatic function panel, complete blood count (CBC), and international normalized ratio (INR) is recommended. | I, C |
| Screening for hepatocellular carcinoma with ultrasound examination every 6 months is recommended for patients with advanced fibrosis (ie, Metavir stage F3 or F4). | I, C |
| Endoscopic screening for esophageal varices is recommended if cirrhosis‡ is present. | I, A |
| Evaluation for retreatment is recommended as effective alternative treatments become available. | I, C |

‡ For decompensated cirrhosis, please refer to the appropriate section.

### The Following Monitoring Is Not Recommended During or After Therapy

| NOT RECOMMENDED | RATING |
|---|---|
| Monitoring for HCV drug resistance-associated substitutions during or after therapy is Not Recommended. | IIb, C |

Patients in whom treatment failed to achieve an SVR remain at risk for ongoing liver injury and progression of liver fibrosis (Dienstag, 2011). Thus, patients in whom treatment fails should be monitored for signs and symptoms of cirrhosis. There is currently no conclusive evidence to suggest that failure of antiviral treatment results in more severe liver injury or more rapidly progressive liver disease than would have occurred if the patient had not received treatment.

Patients in whom an initial antiviral treatment failed have achieved SVR when treated with the same drugs for a longer duration, or when treated with alternative antiviral regimens (Lawitz, 2014a). Thus, patients in whom treatment has failed to achieve an SVR should be considered for treatment when alternative antiviral regimens are available. Advice from a physician experienced in HCV treatment may be beneficial when considering retreatment after antiviral therapy failure.

Patients in whom antiviral therapy failed to achieve an SVR may harbor viruses that are resistant to one or more of the antivirals at the time of virologic “breakthrough” (Lawitz, 2014a); (Schneider, 2014). However, there is no evidence to date that the presence of resistance-associated substitutions (RASs) results in more progressive liver injury than would have

occurred if the patient did not have resistant viruses. The presence of baseline RASs in treatment-naive persons does not preclude achieving an SVR with a combination direct-acting antiviral regimen. Furthermore, RASs are often not detectable with routine (population sequencing) detection methods, nor with more sensitive tests of HCV substitutions, after patients are followed up for several months (Schneider, 2014). Subsequent retreatment with combination antivirals, particularly regimens containing antiviral drugs that have a high barrier to resistance, such as nonstructural protein 5B (NS5B) nucleotide polymerase inhibitors (eg, sofosbuvir), may overcome the presence of resistance to one or more antivirals.

There are three situations in which baseline testing for RASs is recommended in the treatment of HCV genotype 1 infection. First, for those patients whose prior treatment regimen containing an NS5A inhibitor failed and who have cirrhosis or require urgent retreatment, testing for RASs that confer decreased susceptibility to NS3 protease inhibitors (eg, Q80K) and to NS5A inhibitors should be performed using commercially available assays. In a pilot study of 41 patients with or without cirrhosis who did not achieve an SVR with 8 weeks or 12 weeks of therapy with the daily fixed-dose combination of ledipasvir (90 mg) and sofosbuvir (400 mg) (hereafter ledipasvir/sofosbuvir) who were retreated with 24 weeks of ledipasvir/sofosbuvir, rates of SVR at 12 weeks varied according to the presence or absence of certain NS5A inhibitor RASs. Among 11 patients in whom NS5A inhibitor RASs were not detected, SVR occurred in 11 of 11 (100%); in contrast, among 30 patients in whom certain NS5A inhibitor RASs were detected, SVR occurred in 18 of 30 (60%). Importantly, NS5B inhibitor RASs (eg, S282T) known to confer decreased activity of sofosbuvir were observed in 3 of 12 (25%) patients for whom the retreatment regimen was not successful. The additional finding of the Q80K substitution has implications for the retreatment regimen selected for these patients (see Retreatment of Persons in Whom Prior Therapy Has Failed).

Second, for those treatment-naive or PEGIFN/ribavirin-experienced persons with genotype 1a HCV who are being treated with elbasvir/grazoprevir, the presence of baseline NS5A RASs significantly reduces rates of SVR 12 using a 12-week elbasvir/grazoprevir regimen (Zeuzem, 2017). NS5A RASs were identified at baseline in 12% (19/154) of genotype 1a-infected patients enrolled in the C-EDGE study of which 58% (11/19) achieved SVR12 compared to an SVR12 rate of 99% (133/135) in patients without these RASs receiving 12 weeks of elbasvir/grazoprevir (Zeuzem, 2017). Among treatment-naive patients, the presence of baseline NS5A RASs with a larger than 5-fold shift to elbasvir was associated with the most significant reductions in SVR 12 with only 22% (2/9) of genotype 1a patients with these high fold-change RASs achieving SVR12. The recommendation to extend duration of treatment to 16 weeks with inclusion of ribavirin for treatment-naive genotype 1a patients with baseline NS5A RASs is based on extrapolation of data from the C-EDGE TE trial (Kwo, 2015). Based on known inferior response in patients with presence of baseline high fold-change NS5A RASs, NS5A resistance testing is recommended in genotype 1a patients who are being considered for therapy with elbasvir/grazoprevir. If baseline high fold-change RASs are present, ie, substitutions at amino acid positions 28, 30, 31, or 93, treatment extension to 16 weeks with the addition of weight-based ribavirin (1000 mg [<75 kg] to 1200 mg [≥ 75 kg]) is recommended to decrease relapse (see Initial Treatment of HCV Infection or Retreatment of Persons in Whom Prior Therapy Has Failed sections).

Third, for treatment-naive patients or those experienced with PEG-IFN/ribavirin who have HCV genotype 1a infection and cirrhosis, testing for the Q80K NS3 RAS is recommended when simeprevir and sofosbuvir are being considered as treatment. In the OPTIMIST-2 study, in which patients with cirrhosis were treated with simeprevir and sofosbuvir, the presence of NS3 RASs, specifically the Q80K substitution, was associated with a decreased SVR rate. SVR occurred in 25 of 34 (74%) patients with HCV genotype 1a infection and the Q80K RAS and in 35 of 38 (92%) patients with HCV genotype 1a infection without the Q80K RAS (see Initial Treatment of HCV Infection or Retreatment of Persons in Whom Prior Therapy Has Failed sections).

NS5A RAS testing is also recommended in persons with genotype 3 HCV who are considering treatment with sofosbuvir/velpatasvir or daclatasvir/sofosbuvir-based regimens. Baseline NS5A substitutions in genotype 3 impact DAA treatment response, with the Y93H substitution being most problematic. In the ALLY-3 study the Y93H was detected in 13 (9%) of patients with an SVR12 of 54% (7/13); including a 67% SVR12 in patients without cirrhosis. In the ASTRAL-3 study the Y93H was detected in 25 (9%) of patients with an SVR12 rate of 84% (21/25). Treatment-experienced cirrhotic patients are already recommended to have ribavirin added with or without extension of therapy depending on the specific regimen, thus baseline testing for NS5A RASs in genotype 3 is only recommended for treatment approaches for treatment-naive patients with cirrhosis or treatment-experienced patients without cirrhosis. Pending further data on optimal therapy in the setting of baseline Y93H substitution in these particular patient populations, the addition of ribavirin for patients with cirrhosis is recommended.

If there remains uncertainty regarding the applicability of RAS testing, consultation with an expert in the treatment of HCV infection may be useful.

## Recommended Follow-up for Patients Who Achieve a Sustained Virologic Response (SVR)

| RECOMMENDED | RATING |
|---|---|
| For patients who do not have advanced fibrosis (ie, those with Metavir stage F0-F2), recommended follow-up is the same as if they were never infected with HCV. | I, B |
| Assessment for HCV recurrence or reinfection is recommended only if the patient has ongoing risk for HCV infection or otherwise unexplained hepatic dysfunction develops. In such cases, a quantitative HCV RNA assay rather than an anti-HCV serology test is recommended to test for HCV recurrence or reinfection. | I, A |
| Surveillance for hepatocellular carcinoma with twice-yearly ultrasound examination is recommended for patients with advanced fibrosis (ie, Metavir stage F3 or F4) who achieve an SVR. | I, C |
| A baseline endoscopy is recommended to screen for varices if cirrhosis‡ is present. Patients in whom varices are found should be treated and followed up as indicated. | I, C |
| Assessment of other causes of liver disease is recommended for patients who develop persistently abnormal liver tests after achieving an SVR. | I, C |

‡ For decompensated cirrhosis, please refer to the appropriate section.

With the advent of highly effective HCV antiviral regimens, the likelihood of achieving an SVR among adherent, immunologically competent, treatment-naive patients with compensated liver disease generally exceeds 90%. Of patients who achieved an SVR with PEG-IFN/ribavirin treatment, more than 99% have remained free of HCV infection when followed up for 5 years after completing treatment (Manns, 2013). Thus, achieving an SVR is considered a virologic cure of HCV infection.

SVR typically aborts progression of liver injury with regression of liver fibrosis in most but not all treated patients (Morisco, 2013); (Morgan, 2010); (George, 2009); (Morgan, 2013); (Singal, 2010). Because of lack of progression, patients without advanced liver fibrosis (ie, Metavir stage F0-F2) who achieve an SVR should receive standard medical care that is recommended for patients who were never infected with HCV.

Among patients with advanced liver fibrosis (ie, Metavir stage F3 or F4) who achieve an SVR, decompensated liver disease (with the exception of hepatocellular carcinoma) rarely develops during follow-up, and overall survival is prolonged (Morisco, 2013); (Morgan, 2010); (George, 2009); (Morgan, 2013); (Singal, 2010). Patients who have advanced fibrosis or cirrhosis continue to be at risk for development of hepatocellular carcinoma after achieving an SVR, although the risk in these patients is lower than the risk in persistently viremic patients (Morisco, 2013); (Morgan, 2010); (George, 2009); (Morgan, 2013); (Singal, 2010). Patients with cirrhosis who achieve SVR experience increased survival (compared with patients with cirrhosis who are untreated or in whom treatment fails), but still may be at some risk for hepatocellular carcinoma; thus, they should continue to undergo regular surveillance for hepatocellular carcinoma despite the lowered risk that results after viral eradication (Bruix, 2011). The risk of hepatocellular carcinoma among patients with advanced fibrosis prior to treatment but who have regression to minimal fibrosis after treatment is not known. In the absence of data to the contrary, such patients remain at some risk for hepatocellular carcinoma and should be monitored at regular intervals for hepatocellular carcinoma. Alpha-fetoprotein (AFP) is considered an inadequate screening test for HCC (Bruix, 2011).

Liver fibrosis and liver function test results improve in most patients who achieve an SVR (Morisco, 2013); (Morgan, 2010); (George, 2009); (Morgan, 2013); (Singal, 2010). Bleeding from esophageal varices is rare after an SVR (Morisco, 2013); (Morgan, 2010); (George, 2009); (Morgan, 2013); (Singal, 2010). Patients with cirrhosis should receive routine surveillance endoscopy for detection of esophageal varices if not previously done and these should be treated or followed up as indicated (Garcia-Tsao, 2007).

Patients in whom an SVR is achieved but who have another potential cause of liver disease (eg, excessive alcohol use, metabolic syndrome with or without proven fatty liver disease, or iron overload) remain at risk for progression of fibrosis. It is recommended that such patients be educated about the risk of liver disease and monitored for liver disease progression with periodic physical examinations, blood tests, and potentially, tests of liver fibrosis by a liver disease specialist.

Periodically testing patients with ongoing risk for HCV infection (eg, illicit drug use, high-risk sexual exposure) for HCV reinfection is recommended. Flares in liver enzyme test results should prompt evaluation of possible de novo reinfection with HCV through a new exposure (see Management of Acute HCV Infection). Antibody to HCV (anti-HCV) remains positive in most patients following an SVR. Thus, testing for reinfection with HCV is recommended and should be performed with an assay that detects HCV RNA (eg, a quantitative HCV RNA test).

| Monitoring for HCV During Chemotherapy and Immunosuppression | |
|---|---|
| NOT RECOMMENDED | RATING |
| Prospective monitoring for HCV recurrence among patients who achieved a sustained virologic response and who are receiving immunosuppressive treatment (eg, systemic corticosteroids, antimetabolites, chemotherapy, etc) is NOT routinely recommended. | III, C |

Acute liver injury is common among patients receiving chemotherapy or immunosuppressive agents; thus, testing for hepatitis viruses should be included in the laboratory assessment of the cause of liver injury. However, while individuals with inactive (no detectable virus) or past hepatitis B virus infection may experience reactivation and clinically apparent hepatitis during immunosuppressive treatment or chemotherapy, this does not occur with hepatitis C infection. Although some patients with active HCV infection, primarily those with hematologic malignancy, may have a flare in their liver enzymes during chemotherapy, this is unusual (Mahale, 2012). Furthermore, reactivation of past HCV infection, such as after SVR or spontaneous clearance, is not anticipated since there is no residual reservoir for the virus. Thus, in this latter group, routine testing of HCV RNA during immunosuppressive treatment or prophylactic administration of antivirals during immunosuppressive treatment is not recommended.

**Last update:** April 12, 2017

# Not Recommended Regimens In HCV Treatment

**Skip to:** Pregnancy | Decompensated Cirrhosis | Transplant

| Regimens Not Recommended | |
|---|---|
| NOT RECOMMENDED | RATING |
| Daily sofosbuvir (400 mg) and weight-based ribavirin for 24 weeks.[f] | IIb, A |
| PEG-IFN/ribavirin with or without sofosbuvir, simeprevir, telaprevir, or boceprevir. | IIb, A |

| Regimens Not Recommended | |
|---|---|
| Monotherapy with PEG-IFN, ribavirin, or a direct-acting antiviral. | III, A |

[f] Due to fewer options in the posttransplant population, sofosbuvir and ribavirin for 24 weeks is recommended in patients with genotype 2 infection.

Although regimens of sofosbuvir and ribavirin or PEG-IFN/ribavirin plus sofosbuvir, simeprevir, telaprevir, or boceprevir are FDA-approved for particular genotypes, they are inferior to the current recommended regimens. The efficacy of sofosbuvir plus ribavirin for 24 weeks is well demonstrated to be inferior to combination DAA therapy for genotype 1 and 3. For genotype 4, it has not been compared head-to-head with DAA combination therapy, but shorter, well-tolerated DAA combination regimens are now available. The IFN-containing regimens are associated with higher rates of serious adverse events (eg, anemia and rash), longer treatment duration in some cases, high pill burden, numerous drug-drug interactions, more frequent dosing, and higher intensity of monitoring for safety or treatment response.

**Regimens Not Recommended:**

## With Regard to Pregnancy-Related Issues

| NOT RECOMMENDED | RATING |
|---|---|
| Treatment with ribavirin is Not Recommended during pregnancy or for women who are unable or unwilling to adhere to use of adequate contraception, including those who are receiving ribavirin themselves or are sexual partners of male patients who are receiving ribavirin. | III, C |
| Female patients who have received ribavirin and sexual partners of male patients who have received ribavirin should NOT become pregnant for at least 6 months after stopping ribavirin. | III, B |

**Regimens Not Recommended for:**

## Patients with Decompensated Cirrhosis (Moderate or Severe Hepatic Impairment; Child Turcotte Pugh Class B or C)

| NOT RECOMMENDED | RATING |
|---|---|
| Simeprevir-based regimens | III, B |
| Paritaprevir-based regimens | III, B |
| Elbasvir/grazoprevir-based regimens | III, C |

IFN should not be given to patients with decompensated cirrhosis (moderate or severe hepatic impairment; CTP class B or C) because of the potential for worsening hepatic decompensation. Minimal data exist for the use of simeprevir in patients with decompensated cirrhosis (Modi, 2016). Until additional data become available, simeprevir should not be used in patients with decompensated cirrhosis. No data exist for the use of currently approved doses of elbasvir and grazoprevir for patients with decompensated cirrhosis, and this combination should not be used in this population until additional data become available.

Recent data reported by the US FDA have demonstrated that some patients with compensated HCV genotype 1 cirrhosis treated with paritaprevir, ombitasvir, and dasabuvir may develop rapid onset of direct hyperbilirubinemia within 1 to 4 weeks of starting treatment without ALT elevations that can lead to rapidly progressive liver failure and death. A multicenter cohort study from Israel reported 7 patients who received PrOD and also developed decompensation within 1 to 8 weeks of starting therapy, including 1 patient who died (Zuckerman, 2016). Therefore, this antiviral treatment regimen is CONTRAINDICATED in all patients with decompensated HCV cirrhosis due to concerns of hepatotoxicity. In addition, all patients with cirrhosis receiving this regimen should be monitored for clinical signs and symptoms of hepatic decompensation and undergo hepatic laboratory testing at baseline and at least every 4 weeks on therapy.

**Regimens Not Recommended for:**

## Patients with HCV Infection in the Allograft, Including Those with Compensated Cirrhosis

| NOT RECOMMENDED | RATING |
|---|---|
| Elbasvir/grazoprevir-based regimens | III, C |

**Regimens Not Recommended for:**

## Patients with Decompensated Cirrhosis, Who Have HCV Infection in the Allograft

| NOT RECOMMENDED | RATING |
|---|---|
| Regimens containing simeprevir | III, B |
| Fixed-dose combination of paritaprevir, ritonavir, and ombitasvir with or without dasabuvir or ribavirin | III, B |
| Elbasvir/grazoprevir-based regimens | III, C |

**Last update:** July 6, 2016